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Health Effects Assessment for Glycol Ethers

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U.S. Environmental Protection Agency
Office of Research and Development
Office of Health and Environmental Assessment
Environmental Criteria and Assessment Office
Cincinnati, OH 45268

U.S. Environmental Protection Agency
Office of Emergency and Remedial Response
Office of Solid Waste and Emergency Response
Washington, DC 20460

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16. ABSTRACT

This document represents a brief, quantitatively oriented scientific summary of health effects data. It was developed by the Environmental Criteria and Assessment Office to assist the Office of Emergency and Remedial Response in establishing chemical-specific health-related goals of remedial actions. If applicable, chemical-specific subchronic and chronic toxicity interim acceptable intakes are determined for systemic toxicants, or q_1^* values are determined for carcinogens for both oral and inhalation routes.

The glycol ethers for which data were adequate for quantitative assessment include: 2-ethoxyethanol (both inhalation and oral); 2-methoxyethanol (inhalation); diethylene glycol monobutyl ether (oral); ethylene glycol monobutyl ether (inhalation); propylene glycol monomethyl ether (inhalation and oral); and propylene glycol monoethyl ether (oral).

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with glycol ethers. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1^*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

For the purpose of this document, the glycol ethanes were divided into three subclassifications. The first classification is the low molecular weight ethylene glycol ethers, 2-methoxyethanol and 2-ethoxyethanol. These compounds appear to have similar toxic effects when tested in laboratory animals. Of the two, 2-methoxyethanol appears to be more toxic. Data were not sufficient to derive an oral AIS or AIC for 2-methoxyethanol because NOELs for fetotoxicity had not been defined by the available studies. A CS of 22 for teratogenicity in mice was calculated for 2-methoxyethanol administered by gavage during gestation. For 2-ethoxyethanol, an oral AIS of 32.6 mg/day has been calculated from a teratogenicity study in rats. An AIC of 25 mg/day is calculated based on a chronic gavage study in rats. The AIS and AIC calculated for 2-ethoxyethanol may not be protective for 2-methoxyethanol.

An inhalation AIS for 2-methoxyethanol of 4.1 mg/day was calculated based on a NOEL for fetoxicity in rats. An AIC value of 1.7 mg/day is estimated based on subchronic inhalation data. For 2-ethoxyethanol an AIS of 4.8 mg/day and an AIC of 3.5 mg/day are based on teratology and subchronic inhalation data, respectively. A CS for 2-ethoxy ethanol of 12.7 is calculated based on fetotoxicity following inhalation exposure.

The second subclass of glycol ethers consists of the ethylene glycol ethers with higher molecular weight. Although there are a large number of other ethylene glycol ethers, few have been studied in detail. In general, they seem to be less potent toxins than 2-methoxyethanol and 2-ethoxyethanol. It seems probable that wide variability may exist in the toxic potencies of members of this subclass. For example, ethylene glycol dimethyl ether appears to be less toxic than diethylene glycol monomethyl ether. Data were insufficient for calculation of an AIS or AIC for ethylene glycol dimethyl ether. An AIS of 350 mg/day and an AIC of 140 mg/day for oral exposure have been calculated for diethylene glycol monomethyl ether from subchronic and chronic studies, respectively. Data were inadequate for inhalation exposure. This AIS and AIC should be protective for diethylene glycol monomethyl ether, but not necessarily for other members of the subclass or for the subclass as a whole.

Inhalation data for the subclass other ethylene glycol ethers were available only for ethylene glycol monobutyl ether. An inhalation AIS of 11.2 mg/day and an AIC of 1.1 mg/day for ethylene glycol monobutyl ether were calculated from a subchronic study. A CS of 19 was calculated based on increased mortality in guinea pigs exposed by inhalation. Because it is likely that great variation exists in the toxic potencies of members of this subclass, these recommendations should not be applied to other ethylene glycol ethers or to the subclass as a whole.

Propylene glycol ethers are the third subclass of glycol ethers. Oral studies have been performed with propylene glycol monomethyl ether and propylene glycol monoethyl ether. Both compounds appear to have equivalent toxic potencies. An oral AIS of 476 mg/day was calculated for propylene glycol monoethyl ether and of 475 for the monomethyl ether, based on subchronic studies. AICs of 48 and 47 mg/day of the respective isomers for chronic oral exposure were estimated from these same studies.

Inhalation studies were performed only with propylene glycol monomethyl ether. An AIS of 342 mg/day was calculated based on a subchronic study in rats. An AIC of 34.2 mg/day was calculated from the same data. A CS of 10 was calculated based on increased mortality in rats.

Oral studies indicated that propylene glycol monomethyl ether and propylene glycol monoethyl ether are roughly equivalent in toxic potency. If this is also true for inhalation exposure, the AIS and AIC calculated for propylene glycol monomethyl ether should be protective for propylene glycol monoethyl ether as well. Subchronic inhalation studies, however, indicate that dipropylene glycol monomethyl ether may be more toxic than the monopropylene glycol ethers investigated. Therefore, the AIS and AIC calculated for propylene glycol monomethyl ether may not be protective for other members of this subclass or for the subclass as a whole.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BUN	Blood urea nitrogen
bw	Body weight
CAS	Chemical Abstract Service
CNS	Chemical Abstract Service
CS	Composite score
GI	Gastrointestinal
LOAEL	Lowest-observed-adverse-effect level
MCV	Mean corpuscular volume
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
pvc	Packed cell volume
RBC	Red blood cell
RV_d	Dose-rating value
RV_e	Effect-rating value
SG	Specific gravity
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average
WBC	White blood cell

1. ENVIRONMENTAL CHEMISTRY AND FATE

Ethers of glycols with monohydric, dihydric and polyhydric alcohols are called glycol ethers; however, glycol ethers with dihydric and polyhydric alcohol are commonly classified as glycols. Therefore, only a few ethers of glycols with monohydric alcohols will be discussed here. Selected physical and chemical properties of a few glycol ethers are shown in Table 1-1.

Pertinent information pertaining to the fate and transport of the glycol ethers in the atmosphere could not be located in the available literature. It has been suggested by Graedel (1978) that both singlet oxygen and hydroxyl radicals in the atmosphere may react with aliphatic ethers; however, the rate constants for these reactions for the listed glycol ethers are not available. The photochemical reactivities of a few glycol ethers in the lower atmosphere in the presence of NO_x (nitrogen oxides) were studied by Yanagihara et al. (1977). These authors determined that the glycol ethers have high reactivities in the atmosphere under smog conditions. The reac- tivities of the glycol ethers ranged between xylene and toluene reactivities. Based on this information and the residence times of toluene and xylene in the atmosphere (Singh et al., 1981), it has been speculated that the half-life of the glycol ethers in the atmosphere may be <1 day. Because of their high water solubilities, all the glycol ethers listed in Table 1-1, with the exception of 2-phenoxyethanol, are probably significantly removed from air through wet deposition.

Pertinent information regarding the fate and transport of glycol ether in aquatic media could not be located in the literature. Based on the vapor pressures and the water solubilities of these compounds, it is unlikely that volatilization will play an important role in determining the fate of these chemicals in aquatic media. From the rate constant ($\sim 10^9$ M^{-1} sec^{-1})

TABLE 1-1

Selected Physical and Chemical Properties of a Few Glycol Ethers[a]

Compound	Molecular Weight	CAS Number	Vapor Pressure at 25°C (mm Hg)	Water Solubility at 25°C	log K_{ow} [b]
Ethylene glycol monomethyl ether or 2-methoxyethanol	76.1	109-86-4	9.5	completely miscible	-0.74
Ethylene glycol monoethyl ether or 2-ethoxyethanol	90.1	110-80-5	5.5	completely miscible	-0.21
Ethylene glycol n-butyl ether or 2-butoxyethanol	118.2	111-76-2	0.88	completely miscible	0.85
Ethylene glycol phenyl ether or 2-phenoxyethanol	138.2	122-99-6	0.03	2.3 mℓ/100 mℓ	NA
Propylene glycol monomethyl ether or 2-methoxy propanol	90.1	107-98-2	12.5	completely miscible	NA
Diethylene glycol methyl ether or 2-(β-methoxy-ethoxy) ethanol	120.1	111-77-3	0.25	comletely miscible	-0.79 to -0.93

TABLE 1-1 (cont.)

Compound	Molecular Weight	CAS Number	Vapor Pressure at 25°C (mm Hg)	Water Solubility at 25°C	log K_{ow} [b]
Diethylene glycol ethyl ether or 2-(ß-ethoxy-ethoxy) ethanol	134.2	111-90-0	0.26	completely miscible	NA
Diethylene glycol n-butyl ether or 2-(ß-butoxy-ethoxy) ethanol	162.2	112-34-5	0.06	completely miscible	0.15-0.40

[a]Source: Dow Chemical Co., 1981

[b]Octanol/water partition coefficient values obtained from Konemann, 1981; Verschueren, 1983

NA = Not available

values given by Dorfman and Adams (1973), it is unlikely that reaction of hydroxyl radicals with the glycol ethers in aquatic media would be a significant process. The reaction rate constants for the more probable peroxy radical reactions and direct photochemical reactions are not available. The available studies indicate that these compounds may biodegrade in aquatic media (Bridie et al., 1979; Fincher and Payne, 1962; Dow Chemical Co., 1981). The microbial degradation rates may be rapid for some compounds (e.g., ethylene glycolmonomethyl and monoethyl ether) and slow for others (i.e., propylene glycol monomethyl ether). Data in the available literature are insufficient to permit assessment of the most probable fate of these chemicals in aquatic media.

Very little information is available in the literature regarding the fate of glycol ether in soils. Based on the physical properties of these compounds and the available biodegradation studies (Fincher and Payne, 1962), it can be speculated that biodegradation and leaching may play significant roles in determining the fate of these chemicals in soils. Their mobility in soils is expected to be maximal in sandy soils with low organic carbon content due to low soil sorption characteristics for these soils.

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

2.1.1. 2-Methoxyethanol and 2-Ethoxyethanol. Miller et al. (1983a, 1984) administered doses of 1 or 8.7 mmol of ^{14}C- or ^{13}C-2-methoxyethanol labeled at C_1 or C_2 to mature male Fischer 344 rats by gavage. Expired air and urine and feces were collected for the subsequent 48 hours, at which time the rats were killed. The percentage of the total dose of radioactivity recovered was 54.3-63.2% from the urine, 11.8-11.9% from expired CO_2, 0.3-0.4% from exhaled volatiles trapped on activated charcoal and 16.2-21.8% from the whole carcass. Fecal excretion accounted for only 2.6-2.7% of the total dose of radioactivity. Absorption of 2-methoxyethanol from the GI tract was essentially complete.

Similar results were reported by Foster et al. (1984), who administered a single 500 mg/kg bw dose of ^{14}C-2-methoxymethanol (labeled methoxy group) by gavage to rats. After 48 hours, 70% of the dose of radioactivity was recovered from the urine, 2.7% from exhaled air and 12.5% from the tissues. Only 1.5% of the dose was recovered from the feces.

Cheever et al. (1984) demonstrated that absorption of 2-ethoxyethanol is nearly complete. These researchers administered a single 230 mg/kg bw dose of ^{14}C-ethoxyethanol (labeled in the ethanol or ethoxy group) to mature male rats, and collected urine, expired air and feces for up to 96 hours after treatment. Radioactivity in the urine accounted for 75.6-80.6%, in expired air for 4.8-12.1% and in the carcass for 1.8-4.6% of the total dose administered. Fecal excretion accounted for only 2.7-4.5%.

2.1.2. Other Ethylene Glycol Ethers. Oral administration of diethylene glycol monoethyl ether to one human subject was followed by recovery of 68% in the urine as the metabolite (2-ethoxy-ethoxy) acetic acid, indicating

extensive absorption from the GI tract (Kamerling et al., 1977). Details of the protocol were not reported.

Gadaskina and Rudi (1976) administered 400 mg of ethylene glycol monovinyl ether/kg bw (species not stated) and recovered ethylene glycol in the urine over the following 24 hours, which they felt represented complete hydrolysis of 24% of the dose of ethylene glycol monovinyl ether given.

By studying the metabolism of [^{14}C]-labeled ethylene glycol isopropyl ether, Hutson and Pickering (1971) determined that 88% of the compound was excreted from the body within 24 hours following an oral dose. Urinary excretion accounted for 73%, while 14% was excreted by the lungs. These data suggest that absorption following oral administration is rapid and complete; however, digestion or microbial breakdown in the gut or enterohepatic recirculation have not been considered.

2.1.3. Propylene Glycol Ethers. Propylene glycol monomethyl ether also appears to be extensively absorbed, although the metabolism and excretion appear to differ from these processes for the low molecular weight ethylene glycol ethers. Miller et al. (1983a) administered a single gavage dose of 1-^{14}C- and 1-^{13}C-propylene glycol monomethyl ether at 1.0 or 8.7 mmol/kg (90.1 or 780 mg/kg bw) to mature male Fischer 344 rats. Urine, feces and expired air were collected for 48 hours. A total of 11.2-24.8% of the total dose of radioactivity was recovered from the urine, 63.4-66.0% from expired air and only 0.9-1.5% from the feces. Upon sacrifice, the carcass and skin were found to contain 7.7-10.9% of the total dose.

2.2. INHALATION

2.2.1. 2-Methyoxyethanol and 2-Ethoxyethanol. Dajani (1969) found that plasma levels of 2-ethoxyethanol in rats increased nearly linearly with exposures for 1, 2, 4 and 6 hours to 3317 ppm of glycol monoethyl ether.

Extending the exposure time to 8 hours resulted in a near doubling of the plasma levels, indicating saturation of the metabolic pathways and substantial absorption following inhalation exposure.

2.2.2. Other Ethylene Glycol Ethers. Carpenter et al. (1956) demonstrated that butoxyacetic acid is a metabolite of ethylene glycol monobutyl ether in several laboratory species and man, and they have developed a method for estimating the concentration of butoxyacetic acid in urine that may indicate exposure to ethylene glycol monobutyl ether by any route. Substantial quantities of butoxyacetic acid were found in the urine of dogs, monkeys and humans exposed to atmospheres containing 100-385 ppm ethylene glycol monobutyl ether (duration of exposure not specified).

2.2.3. Propylene Glycol Ethers. Absorption data for the propylene glycol ethers by the inhalation route could not be located in the available literature.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral.

3.1.1.1. 2-METHOXYETHANOL AND 2-ETHOXYETHANOL -- Reports of toxicity related to subacute oral exposure of animals to 2-methoxyethanol and 2-ethoxyethanol are summarized in Table 3-1. Many of the early studies are reported incompletely.

2-Methoxyethanol and 2-ethoxyethanol appear to have similar spectra of toxicity, causing depression of RBC, reduced fertility and testicular degeneration (Nagano et al., 1984; Stenger et al., 1971; Lamb et al., 1984; Zenick et al., 1984a,b; Oudiz et al., 1984). Reduced appetite and body weight were also reported (Smyth et al., 1951; Union Carbide, n.d.). For 2-methoxyethanol the effects on the testis of the rat appeared to occur at a lower dose (179 mg/kg bw/day) than did effects on the blood cells (357 mg/kg bw/day) in a 5-week study (Nagano et al., 1984). Chapin et al. (1984) demonstrated that testicular effects are a very sensitive endpoint of 2-methoxyethanol intoxication in the rat. These researchers noted a marked increase in necrotic spermatocytes in rats within 24 hours of a single 150 mg/kg bw dose. Foster et al. (1983) noted degeneration of primary spermatocytes within 24 hours in rats treated with 100 mg/kg bw. In 11-day studies comparing the toxicity of 2-methoxyethanol and 2-ethoxyethanol, a dose of 500 mg/kg bw/day of 2-ethoxyethanol caused the same effect on the testes of rats as did a dose of 100 mg/kg bw/day of 2-methoxyethanol (Creasy et al., 1984; Foster et al., 1984). Zenick et al. (1984a,b) and Oudiz et al. (1984) demonstrated that the effects of 2-ethoxyethanol on the testes are reversible. Five daily doses of 1872 or 2808 mg/kg bw resulted in aspermia by week 7. Recovery was partial to complete by 14 weeks after treatment.

TABLE 3-1

Subchronic Oral Studies with 2-Methoxyethanol and 2-Ethoxyethanol

Compound	Species/Strain	Exposure	Dose (mg/kg bw/day)	Response	Reference
2-Methoxyethanol	mice/JCL-ICR	0, 62.5, 125, 250, 500, 1000, 2000 mg/kg bw, 5 days/week for 5 weeks by gavage	44.6, 89.3, 179, 357 714, 1429	≥179 mg/kg: dose-related testicular atrophy ≥357 mg/kg: dose-related decrease in RBC, WBC	Nagano et al., 1984
2-Methoxyethanol	hamsters/ Syrian golden	0, 62.5, 125, 250, 500 mg/kg bw/day 5 days/week for 5 weeks by gavage	44.6, 89.3, 179, 357	All treatment groups: dose-related decrease in relative testicular weight, no effect on WBC	Nagano et al., 1984
2-Methoxyethanol	guinea pigs/NR	0, 250, 500 mg/kg bw/day, 5 days/week for 5 weeks	179, 357	Both treated groups: marked reduction in relative testicular weight and WBC	Nagano et al., 1984
2-Ethoxyethanol	rats/NR	90 days in drinking water	210[a] 740[a] 1890[a]	No effect Reduced appetite and growth; altered liver and kidney weights Mortality	Smyth et al., 1951
2-Ethoxyethanol	rats/NR	90 days, diet	125[b] 625[b]	No adverse effects Body weight depression	Union Carbide Corp., n.d.
2-Ethoxyethanol	rats/Wistar	13 weeks, gavage, 7 days/week; dosage given as 0, 50, 100, 200, 100/400, 200/800 µℓ/kg bw/day	0, 46.5, 92.9, 186, 191, 382[c]	No effects Testicular degeneration and reduced hemoglobin and hematocrit	Stenger et al., 1971
2-Ethoxyethanol	dogs/beagle	13 weeks; gelatin capsule, 7 days/week; dosage given as 0, 50, 100 or 200 µℓ/kg bw/day	0, 46.5 ≥92.9 186[d]	No effects Decreased hematocrit and hemoglobin Testicular and kidney degeneration	Stenger et al., 1971
2-Ethoxyethanol	mice/JCL-ICR	0, 500, 1000, 2000, 4000 mg/kg bw/day, 5 days/week for 5 weeks by gavage	357, 714, 1429, 2857	≥714 mg/kg: dose-related testicular atrophy and reduced WBC	Nagano et al., 1984
2-Ethoxyethanol	mice/COBS	0, 0.5, 1.0 or 2.0% in drinking water for 14 weeks (continuous breeding protocol)	1000, 2000, 4000[e]	2.0%: reproduction precluded; females had no fertile matings, male fertility reduced 1.0%: reduced fertility 0 and 0.5%: no effects on fertility	Lamb et al., 1984

TABLE 3-1 (cont.)

Compound	Species/Strain	Exposure	Dose (mg/kg bw/day)	Response	Reference
2-Ethoxyethanol	rats/Long-Evans	0 or 936 mg/kg bw by gavage 5 days/week for 6 weeks	669	Reduced rate of body weight gain, decreased hemoglobin and pcv, decreased sperm count and motility, increased abnormal sperm morphology	Zenick et al., 1984a,b; Oudiz et al., 1984

[a]Assumption: rats drink 35 mℓ of water/day and weigh 0.35 kg

[b]Assumption: rats eat food equivalent to 5% of their body weight/day

[c]Doses calculated from SG=0.929; 100/400, 200/800. Lower dose given for 59 days: higher dose given for 32 days.

[d]Doses calculated from SG=0.929

[e]Assumption: Mice drink 6 mℓ of water/day and weigh 0.03 kg

NR = Not reported; RBC = red blood cells; WBC = white blood cells; pcv = packed cell volume; SG = specific gravity

Hamsters appear to be more sensitive than rats to the effects of 2-methoxyethanol, since effects on the testes were noted at 44.6 mg/kg bw/day, the lowest level tested in a 5-week study (Nagano et al., 1984). 2-Ethoxyethanol has not been tested in hamsters.

In early studies with 2-ethoxyethanol in rats a dose of 210 mg/kg bw/day was associated with no effects (Smyth et al., 1951) and 625 mg/kg bw/day was associated only with body weight depression (Union Carbide, n.d.). These early studies failed to observe the effects on the blood cells and testes characteristic of this chemical. These effects appear to occur at 186 mg/kg bw/day in rats (Stenger et al., 1971), 92.9 mg/kg bw/day in dogs (Stenger et al., 1971) and 714 mg/kg bw/day in mice (Nagano et al., 1984).

It appears that 2-methoxyethanol may also be more toxic than 2-ethoxyethanol to mice as well as rats because testicular atrophy was noted for the 2-methoxyethanol at 179 mg/kg bw/day and for 2-ethoxyethanol at 714 mg/kg bw/day (Nagano et al., 1984).

3.1.1.2. OTHER ETHYLENE GLYCOL ETHERS -- Several subchronic studies of other ethylene and diethylene glycols have been performed and are summarized in Table 3-2. Ethylene glycol dimethyl ether appears to have a spectrum of activity similar to that of 2-methoxyethanol in that mice dosed at 179 mg/kg bw/day had reduced testicular weights and reduced WBC counts (Nagano et al., 1984). Slight testicular atrophy was noted in mice at 357 mg/kg bw/day of ethylene glycol monophenyl ether (Nagano et al., 1979). Nagano et al. (1984) reported no effects on the testes of mice with ethylene glycol monopropyl ether or ethylene glycol monobutyl ether at 2000 mg/kg bw/day or with ethylene glycol monophenyl ether at 1000 mg/kg bw/day when administered by gavage on 5 days/week for 5 days.

TABLE 3-2

Subchronic Oral Studies with Other Ethylene Glycol Ethers

Compound	Species/Strain	Exposure	Dose (mg/kg bw/day)	Response	Reference
Ethylene glycol monobutyl ether	rats/NR	diet, duration unspecified	15 or 62.5 250	No adverse effects Growth depression, increased liver and kidney weights	Carpenter, et al., 1956
Ethylene glycol monobutyl ether	mice/NR	gavage, 5 days/week, 5 weeks	62.5-4000	No significant effects on testes or blood	Nagano et al., 1979
Ethylene glycol dimethyl ether	mice/JCL-ICR	0, 250, 500, 1000 mg/kg bw/day, 5 days/week for 5 weeks by gavage	179, 357, 714	All treated groups: dose-related decrease in relative testicular weight and reduced WBC	Nagano et al., 1984
Ethylene glycol monophenyl ether	mice/NR	gavage, 5 days/week, 5 weeks	357, 714, 1429	Slight testicular atrophy Death of 5/5	Nagano et al., 1979
Diethylene glycol monoethyl ether	rats/NR	30-day, drinking water[a]	210-490 870 1770	No effects Reduced appetite Reduced growth, microscopic lesions in kidney, spleen, liver, testes	Smyth and Carpenter, 1948
Diethylene glycol monoethyl ether	rats/NR	90-day, diet	$\leq$500[b] ~2500[b]	No effects Reduced growth and food intake, slightly impaired renal function, increased kidney and testes weight	Hall et al., 1966
Diethylene glycol monoethyl ether	rats/NR	90-day, diet	~250 ~2500	No effects Reduced hemoglobin, oxaluria	Gaunt et al., 1968
Diethylene glycol monoethyl ether	mice/NR	90-day, diet	185-1000 7000-10,000	No effects Reduced hemoglobin, severe kidney damage, oxaluria	Gaunt et al., 1968

TABLE 3-2 (cont.)

Compound	Species/Strain	Exposure	Dose (mg/kg bw/day)	Response	Reference
Diethylene glycol monoethyl ether	ferrets/NR	duration and method not reported[a]	500-3000	No adverse effects	Butterworth et al., 1976
Diethylene glycol monomethyl ether	rats/NR	30-day, drinking water[a]	190 1830	No effects Reduced growth	Smyth and Carpenter, 1948
Diethylene glycol monomethyl ether	rats/NR	110-day, drinking water	~1000[c] ~3000-5000[c]	No effects Hydropic degeneration of kidney tubules	Kesten et al., 1939
Diethylene glycol monobutyl ether	rats/NR	30-day, drinking water[a]	51 94 650	No effects Reduced appetite Microscopic lesions in liver, kidney, spleen, testes	Smyth and Carpenter, 1948
Diethylene glycol monobutyl ether	rats/NR	109-day, drinking water[a]	~1000[c]	No effects	Kesten et al., 1939
Diethylene glycol monobutyl ether	rats/NR	drinking water study, duration unspecified[a]	3000-5000[c]	Anorexia, starvation, dehydration; death of 3/9, degeneration of renal cortex	Kesten et al., 1939

[a]Protocol incompletely reported

[b]Assumed: Rats eat food equivalent to 5% of their body weight/day

[c]Assumed: Rats drink 35 ml of water/day and weigh 0.35 kg

NR = Not reported

Tyler (1984) reviewed three studies of the subchronic oral toxicity of ethylene glycol monobutyl ether in rats and mice. It appeared that the threshold for testicular degeneration in rats was 200 mg/kg bw/day in a 3-month study (Union Carbide Corporation, 1963). In another study with this compound, 250 mg/kg bw/day resulted in depressed growth and increased liver and kidney weights, but no mention was made of effects on the testicles (Carpenter et al., 1956).

Generally, the diethylene glycols tend to be less toxic than the ethylene glycol ethers (Smyth and Carpenter, 1948; Hall et al., 1966; Butterworth et al., 1976; Browning, 1965; Kesten et al., 1939). Effects include reduced growth, lesions in the liver and kidney and reduced blood hemoglobin concentration (Smyth and Carpenter, 1948; Hall et al., 1966; Kesten et al., 1939). Pigs may be more sensitive to diethylene glycol monoethyl ether than rats or mice, however, only 2-3 pigs per treatment group were tested making these data difficult to interpret (Gaunt et al., 1968).

3.1.1.3. PROPYLENE GLYCOL ETHERS -- The propylene glycol ethers appear to be somewhat less toxic than the ethylene glycol ethers (Table 3-3). For both propylene glycol monomethyl and monoethyl ethers, the threshold for adverse effects appears to be ~680-900 mg/kg bw/day (Smyth and Carpenter, 1948; Rowe et al., 1954).

3.1.2. Inhalation.

3.1.2.1. 2-METHOXYETHANOL AND 2-ETHOXYETHANOL -- Subchronic studies of the inhalation toxicity of 2-methoxyethanol and 2-ethoxyethanol are summarized in Table 3-4. Effects of inhalation exposure include microcytic anemia, leukocytopenia with a granulocytic left shift and microscopic lesions in the testes (Werner et al., 1943a,b; Miller et al., 1982, 1984), and a profound reduction of fertility (Hanley et al., 1984a; Rao et al.,

TABLE 3-3

Subchronic Oral Studies with Propylene Glycol Ethers

Compound	Species/Strain	Exposure	Dose (mg/kg bw/day)	Response	Reference
Propylene glycol monoethyl ether	rats/NR	30-day drinking water	680 2140	No adverse effects Reduced growth, kidney changes	Smyth and Carpenter, 1948
Propylene glycol monomethyl ether	rats/NR	35-day, gavage dose 5 days/week in olive oil	947 2847	No adverse effects Increased liver, kidney weights, congestion and cloudy swelling of liver and kidney tubular epithelium	Rowe et al., 1954
Dipropylene glycol monomethyl ether	rats/NR	35 days*	1090	No adverse effects	Browning, 1965

*Protocol incompletely reported

NR = Not reported

TABLE 3-4

Subchronic Inhalation Studies with 2-Methoxyethanol and 2-Ethoxyethanol

Compound	Species/Strain	Exposure	Dose (mg/kg bw/day)	Response	Reference
2-Methoxyethanol	rabbits/NR	30 ppm, 5 days/week for 13 weeks[b]	NC[a]	Decreased testicular size and histological changes	Miller et al., 1982
2-Methoxyethanol	rabbits/NR	0.3, 10 or 30 ppm, 5 days/week for 13 weeks[b]	NC[a]	No effects on testes	Miller et al., 1982
2-Methoxyethanol	rabbit/New Zealand White	0, 30, 100, 300 ppm, 6 hours/day, 5 days/week for 13 weeks	23.6, 78.7, 236[b]	0-30 ppm: no effect 100 ppm: two females died, cause undetermined 300 ppm: two females and two males died, cause undetermined; testicular degeneration, reduced WBC, RBC, hemoglobin, pcv, platelet count, reduced thymus and testes weights	Miller et al., 1984
2-Methoxyethanol	dogs/NR	750 ppm, 7 hours/day, 5 days/week for 12 weeks	57[c]	Occular and nasal irritation, microcytic anemia, leukopenia, granulocytic left shift, urinary Ca oxalate crystals	Werner et al., 1943a
2-Methoxyethanol	rats/NR	310 ppm, 7 hours/day, 5 days/week for 5 weeks	149[d]	Moderate splenic hemosiderosis, fatty replacement of bone marrow cells, granulocytic left shift	Werner et al., 1943b
2-Methoxyethanol	rat/ Sprague-Dawley	0, 30, 100, 300 ppm, 6 hours/day, 5 days/week for 13 weeks	12.4, 41.3, 123.9[d]	0-30 ppm: no effect 100 ppm: reduced body weight of females 300 ppm: reduced body weight of males and females, reduced relative weight of thymus and testes, severe testicular degeneration, reduced WBC, RBC, hemoglobin, pcv, platelet count	Miller et al., 1984
2-Methoxyethanol	rat/ Sprague-Dawley	0, 30, 100, 300 ppm, 6 hours/day, 5 days/week for 13 weeks	12.4, 41.3, 123.9[d]	0-100 ppm: no effect on fertility 300 ppm: male fertility eliminated; no effect on female fertility	Hanley et al., 1984a; Rao et al., 1983
2-Ethoxyethanol	rats/NR	370 ppm, 7 hours/day, 5 days/week for 5 weeks	211[d]	Hemosiderosis of the spleen, decreased hepatocytocellular cytoplasmic density, granulocytic left shift	Werner et al., 1943b

TABLE 3-4 (cont.)

Compound	Species/Strain	Exposure	Dose (mg/kg bw/day)	Response	Reference
2-Ethoxyethanol	rats/ Sprague-Dawley	0, 25, 100 or 400 ppm, 6 hours/day, 5 days week for 13 weeks	12.2, 49.9, 196[d]	Females had increased lacrimation and mucoid nasal discharge. 400 ppm: some decreases in spleen and pituitary weights judged by the authors as not treatment-related	Barbee et al., 1984
2-Ethoxyethanol	rabbits/New Zealand White	0, 25, 100 or 400 ppm, 6 hours/day, 5 days/week for 13 weeks	23.3, 93.2, 373[b]	All treated groups: increased lacrimation and mucoid nasal discharge 400 ppm: reduced body weights, relative testicular weights; decreased pcv, RBC, hemoglobin	Barbee et al., 1984
2-Ethoxyethanol	dogs/NR	840 ppm, 7 hours/day, 5 days/week for 12 weeks	76[c]	Ocular and nasal irritation, altered hematographs	Werner et al., 1943a

[a]Protocol incompletely recorded.

[b]Assumed: Rabbits weigh 1.13 kg, inhale 1.6 m³/day, 100% absorption

[c]Assumed: Dogs weigh 12.7 kg, inhale 1.5 m³/day, 100% absorption

[d]Assumed: Rats weigh 0.35 kg, inhale 0.26 m³/day, 100% absorption

NR = Not reported; NC = not calculated; pcv = packed cell volume; RBC = red blood cell; WBC = white blood cell

1983). Additionally, increased ocular and nasal irritation were noted (Barbee et al., 1984). No effects were observed in rats or rabbits exposed to 2-methoxyethanol at 30 ppm (12.4 and 23.6 mg/kg bw/day, respectively) for 13 weeks (Miller et al., 1984). In dogs, microcytic anemia and leukocytopenia were noted at 57 mg/kg bw/day for 12 weeks (Werner et al., 1943a). In rats, no effects on reproductive performance were observed at 41.3 mg/kg bw/day for 13 weeks, but 123.9 mg/kg bw/day eliminated reproduction in this species (Hanley et al., 1984a; Rao et al., 1983). Exposure to 123.9 mg/kg bw/day for 10 days caused marked reduction in testicular weight and atrophy of the seminiferous tubules in male rats (Doe et al., 1983).

When exposure is by inhalation, 2-ethoxyethanol appears to have nearly the same toxic potency as 2-methoxyethanol. Altered hematologic parameters and occular and nasal irritation occurred in dogs exposed to 2-methoxyethanol at 57 mg/kg bw/day and 2-ethoxyethanol at 76 mg/kg bw/day (Werner et al., 1943a). Rabbits exposed to 300 ppm 2-methoxyethanol or 236 mg/kg bw/day (Miller et al., 1984) and 400 ppm 2-ethoxyethanol or 373 mg/kg bw/day (Barbee et al., 1984) had altered hematograms and evidence of testicular degeneration.

3.1.2.2. OTHER ETHYLENE GLYCOL ETHERS -- Of the higher molecular weight ethylene glycol ether, experimental data were located only for ethylene glycol monobutyl ether. These experiments are summarized in Table 3-5. In humans, eye and upper respiratory irritation occur at 100 ppm (Carpenter et al., 1956). A concentration of 314 ppm is highly lethal to rats and 375 ppm is lethal to guinea pigs (Carpenter et al., 1956). Erythrocyte fragility as an early manifestation of hemolytic anemia occurs at 77 ppm in rats (Dodd et al., 1983) and at 100 ppm in mice (Carpenter et al., 1956).

TABLE 3-5

Subchronic Inhalation Studies with Ethylene Glycol Monobutyl Ether

Species	Exposure	Dose (mg/kg bw/day)	Response	Reference
Humans	100 or 200 ppm for two 4-hour periods/day separated by 30-minute rest period for "several exposures"	69 or 138[a]	≥100 ppm: nose, throat, eye irritation; altered taste sensation, nausea, urinary excretion of butoxyacetic acid 200 ppm: headache	Carpenter et al., 1956
Rats	203 or 314 ppm, 7 hours/day, 5 days/week for 6 weeks	152 or 235[b]	314 ppm: 15/15 died 203 ppm: no deaths, increased liver weight, RBC fragility, hemoglobinuria	Carpenter et al., 1956
Rats	135 or 320 ppm, 8 hours/day, 5 days/week for 5 weeks	101 or 239[b]	Both levels: decreased density of hepatic cytoplasm decreased RBC, hemoglobin	Werner et al., 1943b
Rats	250 ppm, 7 hours/day, 5 days/week for 6 weeks	187[b]	Hemoglobinuria after only three exposures, increased relative liver and kidney weights	Union Carbide Corporation, 1952
Rats	5, 25 or 77 ppm, 6 hours/day, 5 days/week for 5 or 13 weeks	3.2, 16.0, 49.4[b]	5-25 ppm: no effects 77 ppm: transient decrease in rate of body weight gain in females, decreased RBC in females at 5 but not at 13 weeks	Dodd et al., 1983
Mice	100, 200 or 400 ppm, 7 hours/day, 5 days/week for 6, 12 and 18 weeks	168, 336 or 671[c]	≥100 ppm: increased RBC fragility ≥200 ppm: hemoglobinuria and increased liver weight	Carpenter et al., 1956
Guinea pigs	375 or 500 ppm, 7 hours/day, 5 days/week for 6 weeks	202 or 269[d]	≥375 ppm: increased mortality, decreased rate of body weight gain, increased kidney weight 500 ppm: decreased body weight	Carpenter et al., 1956

TABLE 3-5 (cont.)

Species	Exposure	Dose (mg/kg bw/day)	Response	Reference
Guinea pigs	62, 125 or 250 ppm, 7 hours/day, 5 days/week for 6 weeks	33.4, 67.3 or 135[d]	62-125 ppm: no effects 250 ppm: increased kidney weight	Union Carbide Corporation, 1952
Dogs	415 ppm, 5 hours/day 5 days/week for 12 weeks	35.3[e]	Respiratory and occular irritation, decreased RBC and hemoglobin, increased BUN	Werner et al., 1943a

[a]Assumed: humans inhale 10 m^3 during the workday and weigh 70 kg; 100% absorption

[b]Assumed: rats inhale 0.26 m^3/day and weigh 0.35 kg; 100% absorption

[c]Assumed: mice inhale 0.05 m^3/day and weigh 0.03 kg; 100% absorption

[d]Assumed: guinea pigs inhale 0.23 m^3/day and weigh 0.43 kg; 100% absorption

[e]Assumed: dogs inhale 1.5 m^3/day and weight 12.7 kg; 100% absorption

RBC = Red blood cells; BUN = blood urea nitrogen

Decreased density of hepatic cytoplasm was noted in rats at 101 mg/kg bw/day (Werner et al., 1943b). A concentration of 125 ppm in guinea pigs was the highest level at which effects were not observed (Union Carbide Corporation, 1952). Respiratory and ocular irritation, decreased RBC and hemoglobin, and increased BUN were noted in dogs at 35.3 mg/kg bw/day (Werner et al., 1943a).

3.1.2.3. PROPYLENE GLYCOL ETHERS -- Subchronic inhalation studies with the propylene glycol ethers are summarized in Table 3-6. The propylene glycol ethers appear to be somewhat less toxic than the ethylene glycol ethers. Effects on reproduction have not been observed for these compounds. Inhalation exposure is most likely to result in CNS depression, depressed rate of body weight gain, liver enlargement and histopathological changes in the liver (Rowe et al., 1954; Miller et al., 1984). In rats, rabbits and guinea pigs, no-effect levels of propylene glycol monomethyl ether range from ~1100-1700 mg/kg bw/day (Rowe et al., 1954; Miller et al., 1984). Monkeys appear to be more sensitive to this compound as increased liver weights were elevated at 645 mg/kg bw/day; no effects were observed at 344 mg/kg bw/day (Rowe et al., 1954).

Dipropylene glycol monomethyl ether appears to be more toxic than propylene glycol monomethyl ether as changes in the cytoplasm of hepatocytes occur in monkeys at 151-220 mg/kg bw/day (Rowe et al., 1954).

3.2. CHRONIC

3.2.1. Oral.

3.2.1.1. 2-METHOXYETHANOL AND 2-ETHOXYETHANOL -- Data regarding chronic oral toxicity were located only for 2-ethyoxyethanol. These studies, performed with rats and mice, are summarized in Table 3-7. Degeneration of the seminiferous tubules and slight kidney damage were the only

TABLE 3-6

Subchronic Inhalation Studies with Propylene Glycol Ethyl Ethers

Compound	Species	Exposure	Dose (mg/kg bw/day)	Response	Reference
Propylene glycol monomethyl ether	rabbits and monkeys	800 ppm, 132 exposures over 186 days	ND	No adverse effects	Patty, 1963
	rats and guinea pigs	1500 ppm, 130 exposures over 184 days	ND	No adverse effects	
		3000 ppm, 130 exposures over 184 days		Mild CNS depression	
	rats	10,000 ppm, 2 hours/day for 84 days	2282[a]	Growth depression, CNS depression, increased liver, kidney weight	Rowe et al., 1954
	rats	10,000 ppm, 1 hour/day for 78 days	1141[a]	Slight effect on CNS, no effect on growth, organ or body weights	
	rats	10,000 ppm, 0.5 hour/day for 79 days	570[a]	No effect on behavior, growth, body or organ weights, histology	
	rats	6000 ppm, 7 hours/day for 81 days	4791[a]	Males: 4/10 dead; females: 7/10 dead; deep narcosis with development of tolerance, increased liver weight, increased kidney weight males; no histological change.	
		3000 ppm, 7 hours/day for 141 days	2396[a]	Mild CNS depression; increased liver weight; effect on final body weight, histology, BUN, hematology	
	rats	1500 ppm, 7 hours/day for 141 days	1198[a]	No effect on mortality, behavior, growth, organ weights, BUN, hematology, histology	
	rats	0, 300, 1000 or 3000 ppm, 6 hours/day 5 days/week for 13 weeks	0, 147, 489 1467[a]	0-1000 ppm: no effects 3000 ppm: slightly elevated liver weights, hepatocellular swelling in females; sedation	Miller et al., 1984
	monkeys	10,000 ppm, 5 hours/day for 66 days	2457[a]	Depressed body weight, CNS depression, increased liver weight, moderately severe change in liver and lung histology	Rowe et al., 1954
	monkeys	3000 ppm 7, hours/day for 146 days	1290[a]	Increased liver weights, slight histological changes in lung and liver; no effect on body weight, BUN,hematology	
	monkeys	1500 ppm, 7 hours/day for 146 days	645[a]	Increased liver weight, moderate lung changes; No other effects	
	monkeys	800 ppm, 7 hours/day for 147 days	344[a]	No effects	

TABLE 3-6 (cont.)

Compound	Species	Exposure	Dose (mg/kg bw/day)	Response	Reference
Propylene glycol monomethyl ether	guinea pigs	6000 ppm, 7 hours/day for 80 days	3450[a]	Marked narcosis, depression in growth, slight effect on liver histology	Rowe et al., 1954
	guinea pigs	3000 ppm, 7 hours/day for 130 days	1725[a]	No effects	
	rabbits	6000 ppm, 7 hours/day for 80 days	9133[a]	Narcosis, growth depression, increased lung and and liver weights, slight histological changes in lung, but not liver	
	rabbits	3000 ppm, 7 hours/day for 130 days	4567[a]	Slight increase in liver weight, slight histological changes in lung and liver	
	rabbits	1500 ppm, 7 hours/day for 130 days	2283[a]	Increased liver weight, slight histological changes in lung and liver of females	
	rabbits	800 ppm, 7 hours/day for 132 days	1218[a]	No adverse effects	
	rabbits	0, 300, 1000 or 3000 ppm, 6 hours/day 5 days/week for 13 weeks	0, 280, 932 or 2796	0-1000 ppm: no effects 3000 ppm: sedation	Miller et al., 1984
Dipropylene glycol monomethyl ether	rats	300-400 mg, 7 hour/day, 5 day/week for 140 exposures (~28 week)	281-375[a]	Slight transient narcosis during first weeks; increased liver weight; no effect on growth, other organ weights;mortality, hematology (RBC, WBC differential) or histology (lungs, kidney, heart, testes)	Rowe et al., 1954
	guinea pigs,	300-400 ppm, 7 hours/day, 5 days/week for 130 exposures (~26 week)	203-270[a]	Livers of females showed slight granulation and vacuolization of cytoplasm; no effects on mortality, growth, behavior, organ weights or other histology	Rowe et al., 1954
	rabbits	300-400 ppm, 7 hours/day, 5 days/week for 156 exposures (~31 week)	536-715[a]	Hepatic cytoplasm granulated and vacuolated; no effect on mortality, growth, behavior, organ weights or other histology	Rowe et al., 1954
	monkeys	300-400 ppm, 7 hours/day, 5 day/week for 156 exposures (~31 week)	151-202[a]	Hepatic cytoplasm granulated and vacuolated; no effect on mortality, growth, behavior, hematology, organ weights or other histology	Rowe et al., 1954

[a]Assumptions: Rats inhale 0.26 m^3 air/day and weigh 0.35 kg, absorption = 100%
Monkeys inhale 1.4 mg^3 air/day and weight of 3.5 kg, absorption = 100%
Guinea pigs inhale 0.23 m^3 air and weight of 0.43 kg, absorption = 100%
Rabbits inhale 1.6 m^3 air/day and weight of 1.13 kg, absorption = 100%

ND = Not derived (exposure data were insufficient); RBC = red blood cells; WBC = white blood cells

TABLE 3-7

Chronic Oral Studies with 2-Ethoxyethanol

Species	Exposure	Dose (mg/kg, absorption = 100% bw/day)	Response	Reference
Rats	1.45% in diet for 2 years	725*	Enlarged edemetous testes with seminiferous tubular degeneration in 2/3 of the animals	Morris et al., 1942
Rats	0, 500, 1000 or 2000 mg/kg bw 5 days/week for 103 weeks	0, 357, 714 or 1429	2000 mg/kg: terminated at 17-18 weeks due to high mortality 1000 mg/kg: reduced survival of males 500-1000 mg/kg: reduced body weights in both sexes; adrenal enlargement in males	Melnick, 1984
Mice	0, 500, 1000 or 2000 mg/kg bw 5 days/week for 103 weeks	0, 357, 714 or 1429	2000 mg/kg: terminated at 17-18 weeks due to high mortality 1000 mg/kg: decreased testicular weights 500 mg/kg: no effects reported	Melnick, 1984

*Estimated assuming rats consume 5% of their body weight per day

lesions reported in a 2-year dietary study in rats at 725 mg/kg bw/day (Morris et al., 1942). In a 2-year NCI bioassay, high mortality occurred very early (within 17 weeks) in rats treated by gavage at 1429 mg/kg bw/day (Melnick, 1984). The dead rats had testicular degeneration and gastric ulcers, which was considered to be the immediate cause of death. Reduced body weights (both sexes) and adrenal enlargement (males only) were observed at 357 mg/kg bw/day, the lowest dose tested.

In the NCI bioassay, mice treated by gavage at 1429 mg/kg bw/day also died early in the course of treatment, and had lesions identical to those of the rats treated at the same level (Melnick, 1984). Decreased testicular weights were reported at 714 mg/kg bw/day. No lesions or effects were reported at 357 mg/kg bw/day, but few criteria of toxicity were examined and histopathological examination had not been completed.

3.2.1.2. OTHER ETHYLENE GLYCOL ETHERS -- Chronic oral experiments have been performed only with diethylene glycol monoethyl ether. These studies are summarized in Table 3-8. In rats, effects in the kidneys were most commonly observed (Morris et al., 1942; Hanzlik et al., 1947). Other effects included slight liver damage and interstitial edema of the testis (Morris et al., 1942).

In the 3-generation drinking water study by Smyth et al. (1964), effects were not observed at $\leq$200 mg/kg bw/day. At 950 mg/kg bw/day, adverse effects were seen in the kidneys, spleen and intestine. Additionally, fertility was reduced and calculi were found in the bladder.

Mice appeared to be more resistant than rats to diethylene glycol monoethyl ether because exposure via the drinking water at an intake of 6900 mg/kg bw/day resulted in "no significant adverse effects" (Hanzlik et al., 1957).

TABLE 3-8

Chronic Oral Studies with Diethylene Glycol Monoethyl Ether

Species/ Sex	Exposure	Dose (mg/kg bw/day)	Response	Reference
Rats/NR	2.16% in diet for 2 years	1080[a]	Few oxalate concretions in kidney of one rat, slight liver damage, interstitial edema of testes	Morris et al., 1942
Rats/NR	1% in drinking water for 2 years	1409[b]	4/5 survived to 16-31 months; 1/4 had tubular hydropic degeneration of kidney	Hanzlik et al., 1947
Mice/F	5% in diet for 16 months	6900[b]	"No significant adverse effects"	
Rats/M,F	1.0, 0.2, 0.04 and 0.01% in drinking water for 3 generations (each generation maintained for 2 years)	950, 200, 40 and 10[c]	No effects at $\leq$ 200 mg/kg. At 950 mg/kg adverse effects in kidney, spleen and intestine. Reduced fertility and bladder calculi	Smyth et al., 1964

[a]Assumption: Rats eat food equivalent to 5% of their bw/day.

[b]Based on intake data provided in study

[c]Authors' estimate

NR = Not reported

3.2.1.3. PROPYLENE GLYCOL ETHERS -- Pertinent data regarding the chronic and toxicity of the propylene glycol ethers could not be located in the available literature.

3.2.2. Inhalation.

3.2.2.1. 2-METHOXYETHANOL AND 2-ETHOXYETHANOL -- There are relatively few reports of occupational exposure to 2-methoxyethanol and 2-ethoxyethanol, and these are summarized in Table 3-9. Marinenko (1966) reported increased pulse rate and decreased arterial pressure in women occupationally exposed to 600-800 mg 2-ethoxyethanol/m^3 during the workday. Atmospheres containing 61-3960 ppm 2-methoxyethanol have been associated with headaches, dizziness, CNS depression, cerebral atrophy, personality changes and aplastic anemia and other severe hematological changes (Zavon, 1963; Greenburg et al., 1938).

No investigations of chronic inhalation exposure in animals have been reported in the available literature.

3.2.2.2. OTHER ETHYLENE GLYCOL ETHERS -- Pertinent data regarding the chronic inhalation toxicity of other ethylene glycol ethers could not be located in the available literature.

3.2.2.3. PROPYLENE GLYCOL ETHERS -- Pertinent data regarding the chronic inhalation toxicity of other ethylene glycol ethers could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

The teratogenic and fetotoxic effects of the glycol ethers have been tested extensively in laboratory animals. Administration has been by both the oral and inhalation routes. As in the earlier sections of this chapter, 2-methoxyethanol and 2-ethoxyethanol are grouped together because these

TABLE 3-9

Reports of Toxicity in Humans Chronically Exposed to 2-Ethoxyethanol or 2-Methoxyethanol

Compound	Species	Exposure	Response	Reference
2-Ethoxyethanol	human, female	600-800 mg/m³; occupational	Increased pulse rate, decreased arterial pressure	Marinenko, 1966
2-Methoxyethanol	human	61-3960 ppm 9-10 hour/day, 6 day/week	CNS depression, cerebral atrophy, anemia, hypocellular bone marrow	Zavon, 1963
	human	NR	Headache, dizziness, stomach disorders, ocular irritation, personality changes, aplastic anemia, other hematological changes	Greenberg et al., 1938

NR = Not reported

compounds have similar effects and relative toxic potencies. The other higher molecular weight ethylene glycol ethers are considered separately and the propylene glycol ethers constitute a third class.

3.3.1. Oral.

3.3.1.1. 2-METHOXYETHANOL AND 2-ETHOXYETHANOL -- Teratogenicity and fetotoxicity studies of these compounds are summarized in Table 3-10. 2-Methoxyethanol was administered by gavage to pregnant mice on days 7-14 of gestation. A high dose of 1400 mg/kg bw/day resulted in the mortality of 14% of pregnant dams; survivors failed to produce any litters (Schuler et al., 1984). In another study, doses of 31.25-1000 mg/kg bw/day were administered on days 7-14 of gestation (Nagano et al., 1981, 1984). Reduced fetal body weights were observed at doses ≥125 mg/kg bw/day, but skeletal teratogenic abnormalities were observed in all treated groups in a dose-related manner for both incidence and severity.

2-Ethoxyethanol appears to be a somewhat less potent teratogen and fetotoxin than 2-methoxyethanol. Schuler et al. (1984) observed a 10% maternal mortality in mice treated with 2-ethoxyethanol at 3605 mg/kg bw/day; no litters were produced by survivors. In rats treated by gavage, teratogenic skeletal malformations were observed at doses ≥100 µℓ/kg bw/day (93.1 mg/kg bw/day) but not at lower doses (Stenger et al., 1971). Fetotoxicity (abortions, increased resorptions, reduced mean fetal body weight) was not observed at doses <372 mg/kg bw/day. Both 2-methoxyethanol and 2-ethoxyethanol are teratogenic at doses lower than those associated with maternal toxicity or fetal toxicity.

3.3.1.2. OTHER ETHYLENE GLYCOL ETHERS -- The fetotoxicity of higher molecular weight ethylene glycol ethers was tested in mice. These studies are summarized in Table 3-11. At doses >1000 mg/kg bw/day during gestation,

TABLE 3-10

Teratogenicity and Fetotoxicity of Orally Administered 2-Methoxyethanol and 2-Ethoxyethanol

Compound	Species/Strain	Dose/Exposure	Maternal Response	Progeny Response	Reference
2-Methoxyethanol	mice/CD-1	1400 mg/kg bw/day on days 7-14 of gestation	14% mortality	No litters produced	Schuler et al., 1984
2-Methoxyethanol	mice/JCL-ICR	0, 31.25, 62.5, 125, 250, 500 or 1000 mg/kg bw/day on days 7-14 of gestation	1000 mg/kg/day: leuckocytopenia ≥250 mg/kg/day: reduced rate of body weight gain	250-1000 mg/kg bw/day: severe mortality 125-250 mg/kg bw/day: reduced fetal body weight ≥31.25 mg/kg bw/day: skeletal abnormalities, very severe in higher dose groups	Nagano et al., 1981, 1984
2-Ethoxyethanol	mice/CD-1	3605 mg/kg bw/day on days 7-14 of gestation	10% mortality	no litters produced	Schuler et al., 1984
2-Ethoxyethanol	rats/Wistar	0, 12.5, 25, 50, 100, 200 or 400 µl/kg bw/day on days 1-21 of gestation (0, 11.6, 23.3, 46.6, 93.1, 186 or 372 mg/kg bw/day)*	NR	4000 µl/kg bw/day: increased resorptions, decreased number of live fetuses /litter, reduced mean fetal body weight ≥100 µl/kg bw/day: increased incidence of major skeletal malformations	Stenger et al., 1971

*Calculated from SG=0.931

NR = Not reported

TABLE 3-11

Teratogenicity and Fetotoxicity of Orally-Administered Ethylene Glycol Ethers

Compound	Species/Strain	Dose/Exposure	Maternal Response	Progeny Response	Reference
Ethylene glycol monobutyl ether	mice/CD-1	1180 mg/kg bw/day on days 7-14 of gestation	20% mortality	Reduced percentage of viable litters	Schuler et al., 1984
Ethylene glycol dimethyl ether	mice/NR	250-490 mg/kg bw/day on days 7-10 of gestation	NR	≥480 mg/kg/day: embryonic death ≥350 mg/kg/day: major external and skeletal malformations ≥250 mg/kg/day: growth retardation and skeletal variation	McGregor, 1981
Ethylene glycol dimethyl ether	mice/JCL/ICR	0, 250, 350 or 490 mg/kg bw/day on days 7-10 of gestation	no effects	490 mg/kg/day: increased fetal death ≥350 mg/kg/day: gross CNS and internal malformations ≥250 mg/kg/day: skeletal malformation, retarded ossification (fetotoxicity)	Nagano et al., 1984
Ethylene glycol dimethyl ether	mice/CD-1	2000 mg/kg bw/day on days 7-14 of gestation	26% mortality	No litters produced	Schuler et al., 1984
Ethylene glycol diethyl ether	mice/CD-1	2955 mg/kg bw/day on days 7-14 of gestation	10% mortality	Reduced percentage of viable litters, reduced proportion of live births, reduced birth weight, rate of body weight gain and postnatal survival	Schuler et al., 1984
Diethylene glycol monomethyl ether	mice/CD-1	4000 mg/kg bw/day on days 7-14 of gestation	10% mortality	Reduced percentage of viable litters, reduced neonatal survival	Schuler et al., 1984
Diethylene glycol monoethyl ether	mice/CD-1	5500 mg/kg bw/day on days 7-14 of gestation	14% mortality	Reduced pup birth weight	Schuler et al., 1984
Diethylene glycol monobutyl ether	mice/CD-1	500 mg/kg bw/day on days 7-14 of gestation	No mortality	No efffects	Schuler et al., 1984
Diethylene glycol dimethyl ether	mice/CD-1	3000 mg/kg bw/day on days 7-14 of gestation	41% mortality	No litters produced	Schuler et al., 1984

TABLE 3-11 (cont.)

Compound	Species/Strain	Dose/Exposure	Maternal Response	Progeny Response	Reference
Diethylene glycol diethyl ether	mice/CD-1	3000 mg/kg bw/day on days 7-14 of gestation	No mortality	Slightly increased number of dead pups at birth, slightly decreased birth weight	Schuler et al., 1984
Diethylene glycol dibutyl ether	mice/CD-1	2000 mg/kg bw/day on days 7-14 of gestation	8% mortality	Slightly increased number of dead pups at birth	Schuler et al., 1984
Triethylene glycol dimethyl ether	mice/CD-1	3500 mg/kg bw/day on days 7-14 of gestation	4% mortality	No litters produced	Schuler et al., 1984

NR = Not reported

ethylene glycol monobutyl ether, ethylene glycol dimethyl and diethyl ethers, diethylene glycol monomethyl, monoethyl, dimethyl, diethyl and dibutyl ethers resulted in varying amounts of maternal mortality (0-41%) and fetal mortality (Schuler et al., 1984). These studies were performed at only one dosage level. Diethylene glycol monobutyl ether resulted in no maternal mortality or apparent effects on fertility at 500 mg/kg bw/day, the only level tested.

MacGregor (1981) and Nagano et al. (1984) observed teratogenic effects with ethylene glycol dimethyl ether in fetuses from dams treated on days 7-10 of gestation with $\geq$350 mg/kg bw/day. Evidence of fetotoxicity such as growth retardation, minor skeletal variations and delayed ossification occurred at 250 mg/kg bw/day.

3.3.1.3. PROPYLENE GLYCOL ETHERS -- Pertinent data regarding the teratogenic and fetotoxic effects of the propylene glycol ethers when administered orally could not be located in the available literature.

3.3.2. Inhalation

3.3.2.1. 2-METHOXYETHANOL AND 2-ETHOXYETHANOL -- Table 3-12 summarizes teratogenicity and fetotoxicity studies with 2-methoxyethanol in rats, mice and rabbits. The sensitivity of the erythrocyte of rats to 2-methoxyethanol was demonstrated by Hanley et al. (1984a,b). Exposures as low as 3 ppm, 6 hours/day for 10 days of gestation reduced both hematocrit and blood hemoglobin concentration. In other studies in rats, high exposures (100-300 ppm, 6- to 7-hours/day) during days 9-11 of gestation resulted in severe fetal mortality (Nelson et al., 1984a; Doe et al., 1983; Doe, 1984b). Teratogenic malformations were noted at 50 ppm 2-methoxyethanol (Nelson et al., 1984a; Nelson and Brightwell, 1984; Miller et al., 1983b). At 25 ppm, altered regional brain concentrations of neurochemicals were observed in the

TABLE 3-12

Teratogenicity and Fetotoxicity of 2-Methoxyethanol Administered By Inhalation

Species/Strain	Dose/Exposure	Maternal Response	Progeny Response	Reference
Rats/Fischer-344	0, 3, 10 or 50 ppm, 6 hours/day on days 6-15 of gestation (0, 1.7, 5.8 or 29 mg/kg bw/day)[a]	slight, transient decrease in body weight gain at 50 ppm; dose-related reduction in hematocrit and hemoglobin in all treated groups	50 ppm: slight developmental defects indicated slight fetotoxicity; no teratogenicity at any dose level 0-10 ppm: no effects	Hanley et al., 1984a,b
Rats/ Sprague-Dawley	0, 50, 100 or 200 ppm, 7 hours/day on days 7-15 of gestation (0, 33.7, 67 or 135 mg/kg bw/day)[a]	NR	100-200 ppm: severe fetal mortality 50 ppm: increased resorptions, decreased fetal body weight, increased malformations	Nelson et al., 1984a
Rats/ Sprague-Dawley	0 or 25 ppm, 7 hours/day on days 7-13 or 14-20 of of gestation (0 or 16.9 mg/kg bw/day)[a]	no effects	no biologically significant effects on behavior; altered regional brain concentrations of neurochemicals	Nelson et al., 1984b; Nelson and Brightwell, 1984
Rats/Fisher-344	0, 3, 10 or 50 ppm, 6 hours/day on days 6-15 of gestation (0, 1.7, 5.8 or 29 mg/kg bw/day)[a]	NR	50 ppm: "slight fetotoxic effects" 0-10 ppm: no effects	Miller et al., 1983b
Rats/Wistar	0, 100 or 300 ppm, 6 hours/day on days 6-17 of gestation (0, 57.8 or 173 mg/kg bw/day)[a]	300 ppm: reduced body weight gain 100 ppm: prolonged gestation	300 ppm: no live litters produced 100 ppm: reduced total number of pups, proportion of live pups, reduced weight gain at day 3; no external malformations in any group	Doe et al., 1983; Doe, 1984b
Mice/NR	0, 3, 10 or 50 ppm, 6 hours/day on days 6-15 of gestation (0, 3.9, 13.0 or 65 mg/kg bw/day)[b]	NR	50 ppm: reduced litter size and unilateral testicular hypoplasia of male offspring 0-10 ppm: no effects	Blair, 1982
Mice CF-1	0, 10 or 50 ppm, 6 hours/day on days 6-15 of gestation (0, 13.0 or 65 mg/kg bw/day)[b]	50 ppm: reduced rate of body weight gain 0-10 ppm: no effects	50 ppm: slight skeletal developmental defects indicative of fetotoxicity; no teratogenicity at any dose level 0-10 ppm: no effects	Hanley et al., 1984a,b

TABLE 3-12 (cont.)

Species/Strain	Dose/Exposure	Maternal Response	Progeny Response	Reference
Rabbits/New Zealand White	0, 3, 10 or 50 ppm, 6 hours/day on days 6-18 of gestation (0, 3.3, 11.0 or 55 mg/kg bw/day)[c]	NR	50 ppm: significant increase in resorptions and malformations 0-10 ppm: no effects	Miller et al., 1983b
Rabbits/New Zealand White	0, 3, 10 or 50 ppm, 6 hours/day on days 6-18 of gestation (0, 3.3, 11.0 or 55 mg/kg bw/day)[c]	50 ppm: reduced rate of body weight 0-10 ppm: no effects	50 ppm: increased resorptions, decreased mean fetal body weights, malformations involving organs and skeleton 0-10 ppm: no effects	Hanley et al., 1984a,b

[a]Assumed: Rats inhale 0.26 m³/day and weigh0.35 kg; 100% absorption

[b]Assumed: Mice inhale 0.05 m³/day and weigh 0.03 kg; 100% absorption

[c]Assumed: Rabbits inhale 1.6 m³/day and weigh 1.13 kg; 100% absorption

NR = Not reported

offspring of rats exposed 7 hours/day on days 7-13 or 14-20 of gestation, but no biologically significant effects on behavior were noted (Nelson et al., 1984b; Nelson and Brightwell, 1984).

In mice, 50 ppm 2-methoxyethanol produced reduced litter size and other fetotoxic effects and testicular hypoplasia (Blair, 1982; Hanley et al., 1984a,b). No effects were noted at 10 ppm. Similar findings were reported for rabbits (Miller et al., 1983b; Hanley et al., 1984a,b).

The teratogenicity and fetotoxicity of 2-ethoxyethanol was tested in rats and rabbits, and these experiments are summarized in Table 3-13. 2-Ethoxyethanol appears to have a fetotoxic potency in rats slightly less than that of 2-methoxyethanol. Exposures of 600-1200 ppm during gestation resulted in death of all litters and 200 ppm resulted in death of 34% of delivered offspring (Nelson et al., 1981; Hardin et al., 1981; Andrew and Hardin, 1984; Andrew et al., 1981). Exposure of dams to 100 ppm for 7 days during gestation resulted in altered behavior of offspring (Nelson et al., 1981, 1984c; Nelson and Brightwell, 1984). Retarded skeletal ossification, an indicator of slight fetotoxicity, was observed in the fetuses of rats exposed to 50 ppm during 10 days of gestation (Doe, 1984a). Effects were not noted at 10 ppm.

Rabbits may be somewhat more resistant to the fetotoxic effects of 2-ethoxyethanol. In one study, exposure to 615 ppm for 19 days of gestation led to the total resorption of all litters (Hardin et al., 1981; Andrew and Hardin, 1984). At 160 ppm, increased fetal resorption and teratogenic changes were observed. In another study, however, only minor skeletal changes evident of fetotoxicity were noted in fetuses from rabbits treated at 175 ppm during 13 days of gestation (Doe, 1984a). No effects were noted at 50 ppm.

TABLE 3-13

Teratogenicity and Fetotoxicity of 2-Ethoxyethanol Administered by Inhalation

Species/Strain	Dose/Exposure	Maternal Response	Progeny Response	Reference
Rats/ Sprague-Dawley	900, 1200 ppm, 7 hours/day on days 7-13 of gestation (719 or 958 mg/kg bw/day)[a]	NR	No live offspring delivered; dams treated on days 7-13 and sacrificed on day 20 contained no live fetuses	Nelson et al., 1981
Rats/ Sprague-Dawley	200, 600 ppm, 7 hours/day on days 7-13 or 14-20 of gestation (160, 479 mg/kg bw/day)[a]	NR	600 ppm: complete resorption of litters 200 ppm: 34% of offspring delivered dead	Nelson et al., 1981
Rats/ Sprague-Dawley	0 or 100 ppm, 7 hours/day on days 7-13 or 14-20 of gestation (0 or 80 mg/kg bw/day)[a]	Slightly prolonged gestation (p=0.001)	Reduced activity on rotorod (p=0.002) of offspring treated on days 7-13, reduced performance in avoidance conditioning tests (p=0.004) in offspring treated on days 14-20; altered regional or whole-brain concentrations of neurochemicals	Nelson et al., 1981, 1984c; Nelson and Brightwell, 1984
Rats/Wistar	0, 10, 50 or 250 ppm, 6 hours/day on days 6-15 of gestation (0, 6.8, 34 or 171 mg/kg bw/day)[a]	250 ppm: reduced hemoglobin, hematocrit, MCV 0-50 ppm: no effects	250 ppm: decreased mean fetal body weight, retarded ossification 50 ppm: slight fetotoxicity (retarded ossification) 0-10 ppm: no effects	Doe, 1984a
Rats/Wistar or Sprague-Dawley	0, 200 or 765 ppm, 7 hours/day on days 1-19 of gestation (0, 160 or 611 mg/kg bw/day[a]	750 ppm: reduced rate of body weight gain 200 ppm: no effects	750 ppm: all litters totally resorbed 200 ppm: reduced fetal body weight and crown-rump length; cardiovascular and skeletal malformations	Hardin et al., 1981; Andrew and Hardin, 1984; Andrew et al., 1981
Rats/Wistar or Sprague-Dawley	0, 150 or 650 ppm 3 weeks before mating, followed by 0, 200 or 765 ppm on days 1-19 of gestation; exposures for 7 hours/day (TWA-0, 139 or 563 mg/kg bw/day)[a]	High dose group: reduced rate of body weight gain Low dose group: no effects	High dose group: all litters totally resorbed Low dose group: reduced fetal body weight and crown-rump length; skletal malformations	Hardin et al., 1981; Andrew and Hardin, 1984; Andrew et al., 1981

TABLE 3-13 (cont.)

Species/Strain	Dose/Exposure	Maternal Response	Progeny Response	Reference
Rabbits/New Zealand White	0, 160 or 615 ppm, 7 hours/day on days 1-18 of gestation (0, 244 or 936 mg/kg bw/day)[b]	615 ppm: severe anorexia, weight loss, death of 5/29 160 ppm: anorexia, reduced body weight gain, hepatomegaly	615 ppm: all litters totally resorbed 160 ppm: increased resorptions, major visceral and minor skeletal defects	Hardin et al., 1981; Andrew and Hardin, 1984
Rabbits/Dutch	0, 10, 50 or 175 ppm, 6 hours/day on days 6-18 of gestation (0, 13, 65 or 228 mg/kg bw/day)[b]	No effects	175 ppm: minor skeletal defects (evidence of fetotoxicity) 0-50 ppm: no effects	Doe, 1984a

[a]Assumed: Rats inhale 0.26 m³/day and weigh 0.35 kg; 100% absorption

[b]Assumed: Rabbits inhale 1.6 m³/day and weigh 1.13 kg; 100% absorption

NR = Not reported; MCV = mean corpuscular volume

3.3.2.2. OTHER ETHYLENE GLYCOL ETHERS -- Teratogenic effects were not reported for ethylene glycol monobutyl ether or diethylene glycol monoethyl ether (Tyl et al., 1984; Nelson et al., 1984a) (Table 3-14). When tested at 100 ppm diethylene glycol monoethyl ether, rats showed no evidence of fetotoxicity (Nelson et al., 1984a). The fetotoxicity of ethylene glycol monobutyl ether, however, is not clearly understood. Nelson et al. (1984a) reported no toxicologically significant maternal effects and no effects on the progeny of rats exposed to 200 ppm, 7 hours/day on days 7-15 of gestation. Tyl et al. (1984), on the other hand, noted a reduced rate of body weight gain and reduced RBC in rats exposed to $\geq$100 ppm for 6 hours/day on days 6-15 of gestation. At 200 ppm, increased resorptions were noted and at 100 ppm, there was retarded skeletal ossification, a sign of fetotoxicity. No effects were observed in dams or fetuses at 50 ppm. Possibly, the apparent discrepancies in the studies by Nelson et al. (1984a) and Tyl et al. (1984) may represent differences between strains of rats. Nelson et al. (1984a) used Sprague-Dawley rats and Tyl et al. (1984) used Fischer 344 rats.

Tyl et al. (1984) produced increased mortality and spontaneous abortions in rabbits exposed to 200 ppm ethylene glycol monobutyl ether during days 6-18 of gestation. Fetal effects included reduced implantation, increased resorptions and retarded skeletal ossification. No effects were observed in either dams or fetuses at 100 ppm.

3.3.2.3. PROPYLENE GLYCOL ETHERS -- The teratogenicity and fetotoxicity of propylene glycol monomethyl ether has been investigated in rats and rabbits (Table 3-15). The fetus of the rabbit appears to be resistant as no effects on the fetus were observed when dams were exposed to 3000 ppm, 6 hours/day on days 6-18 of gestation (Hanley et al., 1984b,c). This level

TABLE 3-14

Teratogenicity and Fetotoxicity of Ethylene Glycol Ethers Administered by Inhalation

Compound	Species/Strain	Dose/Exposure	Maternal Response	Progeny Response	Reference
Ethylene glycol monobutyl ether	rats/ Fisher 344	0, 25, 50, 100 or 200 ppm, 6 hours/day on days 6-15 of gestation (0, 22.4, 44.9, 89.8 or 180 mg/kg bw/day)[a]	100 and 200 ppm: clinical signs of maternal toxicity, reduced RBC, reduced rate of body weight gain 0-50 ppm: no effects	200 ppm: increased resorptions ≥100 ppm: retarded skeletal ossification 0-50 ppm: no treatment-related effects	Tyl et al., 1984
Ethylene glycol monobutyl ether	rats/ Sprague-Dawley	0, 150 or 200 ppm, 7 hours/day on days 7-15 of gestation (0, 157 or 209 mg/kg bw/day)[a]	No toxicologically significant effects	No effects	Nelson et al., 1984a
Ethylene glycol monobutyl ether	rabbits/New Zealand White	0, 25, 50, 100 or 200 ppm, 6 hours/day on days 6-18 of gestation (0, 42.8, 86, 171 or 343 mg/kg bw/day)[b]	200 ppm: clinical signs of toxicity and increased and spontaneous abortions (NS) 0-100 ppm: no effects	200 ppm: reduced implantation, increased resorptions, retarded skeletal ossification 0-100 ppm: no treatment-related effects	Tyl et al., 1984
Diethylene glycol monoethyl ether	rats/ Sprague-Dawley	0 or 100 ppm, 7 hours/day on days 7-15 of gestation (0 or 119 mg/kg bw/day)[a]	No effects	No effects	Nelson et al., 1984a

[a]Assumed: Rats inhale 0.26 m³/day and weigh 0.35 kg; 100% absorption

[b]Assumed: Rabbits inhale 1.6 m³/day and weight 1.13 kg; 100% absorption

NS = Not statistically significant

TABLE 3-15

Teratogenicity and Fetotoxicity of Propylene Glycol Ethers Administered by Inhalation

Compound	Species/Strain	Dose/Exposure	Maternal Response	Progeny Response	Reference
Propylene glycol monomethyl ether	Rats/ Fischer 344	0, 500, 1500 or 3000 ppm, 6 hours/day on days 6-15 of gestation (0, 342, 1027 or 2053 mg/kg bw/day)[a]	3000 ppm: CNS depression, decreased food intake and rate of body weight gain 0-1500 ppm: no effect	3000 ppm: slight fetotoxicity (delayed sternebrae ossification) 0-1500 ppm: no effects	Hanley et al., 1984b,c
Propylene glycol monomethyl ether	Rats/Wistar	0, 200 or 600 ppm, 6 hours/day on days 6-17 of gestation (0, 137 or 411 mg/kg bw/day)[a]	No effects	No effects	Doe et al., 1983, 1984b
Propylene glycol monomethyl ether	Rabbits/New Zealand White	0, 500, 1500 or 3000 ppm, 6 hours/day on days 6-18 of gestation (0, 652, 1957 or 3913 mg/kg bw/day)[b]	3000 ppm: transient CNS depression, decreased rate of body weight gain 0-1500 ppm: no effects	No effects	Hanley et al., 1984b,c

[a]Assumed: Rats inhale 0.26 m³/day and weigh 0.35 kg

[b]Assumed: Rabbits inhale 1.6 m³/day and weigh 1.13 kg

caused transient CNS depression and decreased rate of body weight gain in the dams. In rats, delayed sternebral ossification, a mild fetotoxic effect, was observed in fetuses of dams exposed to 3000 ppm for 6 hours/day on days 6-15 of gestation (Hanley et al., 1984b,c). The dams exhibited CNS depression, decreased food intake and decreased rate of body weight gain. No effects were observed at concentrations ≤1500 ppm (Hanley et al., 1984b,c; Doe et al., 1983, 1984b).

3.4. TOXICANT INTERACTIONS

Because of the effects of glycol ethers on the CNS, Budden et al. (1979) investigated the effects of diethylene glycol monoethyl ether on hexabarbitone-induced sleeping time. Oral administration of 0.7 g diethylene glycol monoethyl ether/kg bw to female NMRI mice increased hexabarbitone-induced sleeping time 100%. Similarly, a single 4-hour exposure to 125 ppm ethylene glycol monomethyl ether also increased pentobarbital sleeping time in mice (Goldberg et al., 1962).

The presence of ethylene glycol in diethylene glycol monoethyl ether as a contaminant can markedly affect the apparent toxicity to animals. Smyth et al. (1964) exposed rats for 3 generations (animals were killed after 2 years) to drinking water treated with diethylene glycol monoethyl ether containing <0.2% or 29.5% ethylene glycol. The sample containing 29.5% ethylene glycol was considerably more toxic than the purer grade. The maximum safe dosage for the less pure sample was ~0.01 g/kg/day, but the maximum safe dose for the more pure sample was 0.20 g/kg/day, indicating that ethylene glycol may be several times more toxic than diethylene glycol monoethyl ether.

Nelson et al. (1982, 1984c) tested the influence of ethanol supplied at 10% in the drinking water to modify the neurobehavioral toxicity of 2-ethoxyethanol administered prenatally via inhalation to Sprague-Dawley rats. 2-Ethoxyethanol exposure was at 100 or 200 ppm, 7 hours/day on days 7-13 of gestation or at 200 ppm, 7 hours/day on days 14-20 of gestation. When administered early in gestation (days 7-13), ethanol appeared to reduce the effects of 2-ethoxyethanol on neuromotor behavior, as evidenced by improved performance on the rotorod. Ethanol administered late in gestation (Days 14-20) appeared to intensify the effects of 2-ethoxyethanol, as performance in the open field test was reduced.

In a study of the effects of 2-methoxyethanol on the testes of rats, Foster et al. (1984) administered a 500 mg/kg bw oral dose of 2-methoxyethanol to unpretreated rats or rats pretreated with the alcohol dehydrogenase inhibitor pyrazole or pretreated with the aldehyde dehydrogenase inhibitors disulfiram or pargyline. Rats that were not pretreated had histopathological alterations in the testes consisting of degeneration of the primary spermatocytes. Pyrazole, the alcohol dehydrogenase inhibitor, provided complete protection from the effects of 2-methoxyethanol. No protection was provided by the aldehyde dehydrogenase inhibitors, disulfiram or pargyline.

4. CARCINOGENICITY

4.1. HUMAN DATA

No reports of carcinogenicity in humans exposed to the glycol ethers have been located in the available literature.

4.2. BIOASSAYS

No bioassays of the glycol ethers in animals have been located in the available literature. An NCI gavage bioassay of ethylene glycol monoethyl ether is currently in progress, but results are not yet available (Melnick, 1984).

4.3. OTHER RELEVANT DATA

The mutagenicity of several glycol ethers has been tested in prokaryote and eukaryote systems. Results in the reverse mutation Salmonella typhimurium assay (2-methoxyethanol: McGregor et al., 1983; McGregor, 1983; 2-ethoxyethanol: NTP, n.d.; Kowalek and Andrews, 1980; diethylene glycol monobutyl ether: Thompson et al., 1984; diethylene glycol dimethyl ether: McGregor et al., 1983; propylene glycol methyl ether: Kirkland and Varley, 1983a; Mendrala, 1983a; propylene glycol ethyl ether: Dow Chemical Co., 1982; dipropylene glycol methyl ether: Mendrala, 1983b, Kirkland and Varley, 1983b; tripropylene glycol methyl ether: Mendrala, 1982), in the Escherichia coli reverse mutation assay (Szybalski, 1958) and in a test in Schizosaccharomyces pombe (Abbondandolo et al., 1980) have been consistently negative.

2-Methoxyethanol (McGregor et al., 1983), ethylene glycol monobutyl ether (Tyler, 1982), diethylene glycol monobutyl ether (Thompson et al., 1984), diethylene glycol dimethyl ether (McGregor et al., 1983), propylene glycol methyl ether (Mendrala, 1983c), and dipropylene glycol methyl ether (Mendrala, 1983b) were negative in the cell culture test for unscheduled DNA synthesis.

Results were mixed in the SCE test with CHO cells. 2-Ethoxyethanol produced a positive response (NTP, n.d.) and ethylene glycol monobutyl ether produced a negative response (Tyler, 1982). Similarly, in chromosomal aberration tests with CHO cells, 2-ethoxyethanol was positive (NTP, n.d.), but diethylene glycol monobutyl ether (Thompson et al., 1984), propylene glycol monomethyl ether (Kirkland, 1983a) and dipropylene glycol monomethyl ether (Kirkland, 1983b) were negative.

In tests for point mutations in mouse lymphoma L5178Y cells or CHO cells, negative results were noted for 2-methoxyethanol (McGregor, 1984) and ethylene glycol monobutyl ether (Tyler, 1982) and a weak positive result was obtained for diethylene glycol butyl ether (Thompson et al., 1984). Negative results were obtained with 2-methoxyethanol and diethylene glycol dimethyl ether in tests with rat bone marrow cells (McGregor et al., 1983).

In the sex-linked recessive lethal test in Drosophila, 2-methoxyethanol (McGregor et al., 1983) and diethylene glycol dimethyl ether (McGregor, n.d.) produced inconsistent results. Negative results were obtained with 2-ethoxyethanol (NTP, n.d.) and diethylene glycol monobutyl ether (Thompson et al., 1984). Weakly positive results were obtained for 2-methoxyethanol and diethylene glycol dimethyl ether in the dominant lethal test in male rats (McGregor et al., 1983). These chemicals produced strongly positive results in the mouse sperm abnormality test (McGregor et al., 1983).

4.4. WEIGHT OF EVIDENCE

The results of the NCI gavage bioassay of 2-ethoxyethanol in rats and mice are not yet available. Intraperitoneal administration of triethylene glycol diglycidyl ether, a research antineoplastic chemical, has been significantly ($p<0.001$) associated with increased incidence of lung tumors in A/J mice (Shimkin et al., 1966).

IARC has not evaluated the risks to humans associated with oral or inhalation exposure to the glycol ethers. Applying the criteria proposed by the Carcinogen Assessment Group of the U.S. EPA for evaluating the overall weight of evidence for carcinogenicity to humans (Federal Register, 1984), the glycol ethers are most appropriately designated Group D - Not Classified compounds.

5. REGULATORY STANDARDS AND CRITERIA

Regulatory standards and criteria for glycol ethers are summarized in Table 5-1. The ACGIH (1980) has set the recommended TWA-TLV for 2-methoxyethanol at 5 ppm (~16 mg/m³) based primarily on the effects on reproduction in male rats (Rao et al., 1982). For 2-ethoxyethanol, the ACGIH (1980) recommended a TWA-TLV of 5 ppm, reduced from an earlier high of 50 ppm (based on the analogy of this compound with ethylene glycol ether). The TWA-TLV for ethylene glycol monobutyl ether was recommended at 25 ppm to protect workers from the hemolytic effects of this compound, which have been demonstrated most dramatically in the rat (Werner et al., 1943b; Carpenter et al., 1956). A STEL of 75 ppm for this compound was recommended. The toxicity of propylene glycol monomethyl ether seems to be somewhat less than the toxicity of the ethylene glycol ethers discussed above. To protect workers from the objectionable odors and ocular irritation associated with greater concentrations of propylene glycol monomethyl ether, a TWA-TLV of 100 ppm and a STEL of 150 ppm were recommended. The same criteria were adopted by the ACGIH (1980) for dipropylene glycol monomethyl ether, also to protect workers from objectionable odor which may occur at concentrations >100 ppm. CNS impairment in humans apparently occurs at concentrations of ~1000 ppm.

TABLE 5-1

Regulatory Standards and Criteria for Glycol Ethers

Standard or Criterion	Value	Reference
2-Methoxyethanol		
TWA-TLV	5 ppm (~16 mg/m³)	ACGIH, 1980
OSHA standard	25 ppm (~80 mg/m³)	Code of Federal Regulations, 1981
2-Ethoxyethanol		
TWA-TLV	5 ppm (~18 mg/m³)	ACGIH, 1980
OSHA standard	200 ppm (~740 mg/m³)	Code of Federal Regulations, 1981
Ethylene glycol monobutyl ether		
TWA-TLV	25 ppm (~120 mg/m³)	ACGIH, 1980
STEL	75 ppm (~360 mg/m³)	ACGIH, 1980
OSHA standard	50 ppm (~240 mg/m³)	Code of Federal Regulations, 1981
Propylene glycol monomethyl ether		
TWA-TLV	100 ppm (~360 mg/m³)	ACGIH, 1980
STEL	150 ppm (~540 mg/m³)	ACGIH, 1980
Dipropylene glycol monomethyl ether		
TWA-TLV	100 ppm (~600 mg/m³)	ACGIH, 1980
STEL	150 ppm (~900 mg/m³)	ACGIH, 1980
OSHA standard	100 ppm (~600 mg/m³)	Code of Federal Regulations, 1981

6. RISK ASSESSMENT

Most of the toxicity studies discussed in Chapter 3 were early studies that often used small numbers of experimental animals and inadequate controls. Moreover, the experimental protocol including specific dosage levels was often unclear in the secondary sources from which these studies were cited. Where sufficient data were available, threshold levels were identified.

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

6.1.1. Oral.

6.1.1.1. 2-METHOXYETHANOL AND 2-ETHOXYETHANOL -- The subchronic oral studies with 2-methoxyethanol and 2-ethoxyethanol were summarized in Table 3-1. 2-Methoxyethanol appeared to be somewhat more toxic than 2-ethoxyethanol. Nagano et al. (1984) investigated the toxicity of 2-methoxyethanol in mice, hamsters and guinea pigs by administering the chemical by gavage for 5 weeks. Hamsters appeared to be the species most sensitive to the effects of 2-methoxyethanol on the testes, since a dose-related decrease in testicular weight was observed in all treated groups. The lowest dose tested was 44.6 mg/kg bw/day. In other studies, Nagano et al. (1984) observed terata in mice treated with 2-methoxyethanol during gestation at 31.25 mg/kg bw/day (see Table 3-10). Since these studies were not performed at doses sufficiently low to identify a NOAEL, no AIS can be derived for 2-methoxyethanol.

A CS was calculated for 2-methoxyethanol based on teratogenicity in mice, which occurred at 31.25 mg/kg bw/day in the gavage study by Nagano et al. (1984). The animal dose was multiplied by the cube root of the body weight ratio of mice (assumed: 0.03 kg) to that of humans (assumed: 70 kg)

and by 70 kg to obtain a human MED of 165 mg/day, corresponding to an RV_d of 2.2. The teratogenicity observed was assigned an RV_e of 10, and a CS of 22 was calculated as the product of RV_d and RV_e.

2-Ethoxyethanol was also found to be teratogenic in rats when administered during the gestation period at levels $\geq$93.1 mg/kg bw/day (Stenger et al., 1971) (see Table 3-10). Higher doses reduced fertility. No teratogenic effects were observed at 11.6, 23.3 or 46.6 mg/kg bw/day. In a 13-week gavage study in rats, $\geq$186 mg/kg bw/day resulted in testicular degeneration and effects on the erythrocyte (Stenger et al., 1971) (see Table 3-1). No effects were observed at 46.5 or 92.9 mg/kg bw/day.

An oral AIS for 2-ethoxyethanol can be calculated from a no-effect level in the teratogenicity study in rats by Stenger et al. (1971) because it is clear that all teratogenic no-effect levels are below levels that cause other toxic effects. The NOEL for teratogenic effects of 46.6 mg/kg bw/day is used as the basis for the AIS. An uncertainty factor of 100 is applied, a factor of 10 to reflect the unknowns in interspecies extrapolation and another factor of 10 to protect unusually sensitive individuals. The result is multiplied by 70 kg to result in an AIS for 2-ethoxyethanol of 32.6 mg/day for a 70 kg human.

6.1.1.2. OTHER ETHYLENE GLYCOL ETHERS -- The ethylene glycol ethers other than 2-methoxyethanol and 2-ethoxyethanol can be broadly classified into two groups. The first group consists of other monoethylene glycol ethers such as ethylene glycol monobutyl ether, ethylene glycol monophenyl ether and ethylene glycol dimethyl ether. The second group consists of the di- and triethylene glycol ethers. In the first category, the toxicity of ethylene glycol dimethyl ether seems similar to the toxicity of 2-methoxyethanol and 2-ethoxyethanol, although it may be relatively less potent. In

a 5-week gavage test in mice, a dose-related decrease in relative testicular weights and reduced RBC was noted at all treatment levels (179-714 mg/kg bw/day) (Nagano et al., 1984). At ≥350 mg/kg bw/day during gestation, major internal, external and skeletal malformations were produced (McGregor, 1981; Nagano et al., 1984). Skeletal malformations indicative of fetotoxicity were observed at 250 mg/kg bw/day, the lowest dose tested. Studies were not performed at doses sufficiently low to define no-effect levels of ethylene glycol dimethyl ether. The data base on the other monoethylene glycol ethers is insufficient to identify no-effect levels or to rank their toxic potency relative to that of ethylene glycol dimethyl ether (see Table 3-2). Therefore, an oral AIS is not derived for the monoethylene glycol ethers.

The diethylene glycol ethers appear to be somewhat less toxic than the monoethylene glycol ethers (see Table 3-2). No-effect levels have been determined at 490 mg/kg bw/day for diethylene glycol monoethyl ether (Smyth and Carpenter, 1948), and at 1000 mg/kg bw/day for diethylene glycol monomethyl ether (Kesten et al., 1939). The toxicity of diethylene glycol monobutyl ether is not as clear, since 1000 mg/kg bw/day yielded no effects in one study in rats (Kesten et al., 1939), but 650 mg/kg bw/day led to microscopic lesions in the liver, kidney, spleen and testes of rats in another study (Smyth and Carpenter, 1948). Organoleptic effects were observed in the latter study at 94 mg/kg bw/day.

Schuler et al. (1984) investigated the fetotoxicity of several diethylene glycol ethers in mice. High doses during days 7-14 of gestation were used which were designed to cause ~10% maternal mortality, and in all but one case resulted in maternal mortality ranging from 4-41%. A spectrum of effects indicative of fetotoxicity were reported. However, this is not surprising considering that testing was in the range of doses associated

with maternal mortality. Additional testing at lower doses would be desirable. The NOEL of 500 mg/kg bw/day (Hall et al., 1966) for diethylene glycol monoethyl ether, may be used to derive an AIS for this compound. This is supported by a NOEL of 490 mg/day from Smyth and Carpenter (1948). An uncertainty factor of 100 is applied, a factor of 10 for interspecies conversion and another factor of 10 to protect unusually sensitive individuals. Multiplying the result by 70 kg results in an AIS for diethylene glycol monoethyl ether of 350 mg/day for a 70 kg human.

This AIS should also be protective for diethylene glycol monomethyl ether. Alternatively, a separate value for diethylene glycol monomethyl ether could be calculated from the NOEL of 1000 mg/kg (Kesten et al., 1939). The reporting of this study was incomplete and the sole other report concerning the subchronic toxicity of this compound was a study of only 30 days duration, reported in even less detail. In addition, in a fetotoxicity evaluation, Schuler et al. (1984) reported 10% maternal mortality following only 7 days of dosing of rats with 4000 mg/kg. In view of these concerns, and also considering that the value derived for diethylene glycol monoethyl ether would only over-estimate the AIS by a factor of 2 if following further testing the NOEL of 1000 mg/kg is supported, it is suggested that the AIS of 343 mg/day based on diethylene glycol monoethyl ether serve as an interim value for the monomethyl ether as well.

6.1.1.3. **PROPYLENE GLYCOL ETHERS** -- The subchronic oral toxicity of propylene glycol monomethyl ether and propylene glycol monoethyl ether have been investigated in rats (see Table 3-3). Although these studies are only marginally adequate for risk assessment, it appears that a NOEL for the former compound is ~900 mg/kg bw/day (Rowe et al., 1954) and for the latter is 680 mg/kg bw/day (Smyth and Carpenter, 1948). An oral AIS for the propylene glycol monoethyl ethers can be calculated from the NOEL of 680 mg/kg

bw/day for propylene glycol monoethyl ether by applying an uncertainty factor of 100 (10 for interspecies conversion and 10 to protect unusually sensitive individuals) and multiplying the result by 70 kg. An AIS for the propylene glycol monoethyl ether of 476 mg/day for a 70 kg human is calculated, which should be protective for the propylene glycol monomethyl ether as well. An AIS for propylene glycol monomethyl ether may be calculated from the NOEL of 949 mg/kg by multiplying by 5 days/7 days and applying an uncertainty factor of 100, results in an AIS of 474.5 mg/day.

6.1.2. Inhalation.

6.1.2.1. 2-METHOXYETHANOL AND 2-ETHOXYETHANOL -- The subchronic inhalation toxicity of 2-methoxyethanol has been tested in rats, dogs and rabbits (see Table 3-4). The highest NOEL below which effects were not seen was 30 ppm in rabbits, 6 hours/day, 5 days/week for 13 weeks. This exposure corresponds to a dose of 23.6 mg/kg bw/day (Miller et al., 1984) (see Table 3-4 for dose conversion procedure). In teratogenicity and fetotoxicity studies (see Table 3-12), developmental defects and "slight fetotoxic effects" were observed in rats at 50 ppm, 6 hours/day on days 6-15 of gestation (Hanley et al., 1984a,b; Miller et al., 1983b). This exposure corresponds to a maternal dose of 29.0 mg/kg bw/day, which is similar to the NOEL of 23.6 mg/kg bw/day from the subchronic inhalation studies. The NOEL for fetotoxicity in the Hanley et al. (1984a,b) and Miller et al. (1983b) studies is 10 ppm (5.8 mg/kg bw/day), 5-fold less than the LOAEL.

In a study of behavioral and neurochemical alterations resulting from prenatal exposure to 2-methoxyethanol, exposure to 25 ppm (16.9 mg/kg bw/day) led to no biologically significant effects on behavior, but appeared to result in altered regional brain concentrations of neurochemicals (Nelson et al., 1984b, Nelson and Brightwell, 1984). The NOEL for fetotoxicity of 5.8 mg/kg bw/day from the studies of Hanley et al. (1984a,b) and Miller et

al. (1983b) is therefore chosen with confidence that is it also a NOEL for subchronic toxic effects from which to derive an inhalation AIS for 2-methoxyethanol. An uncertainty factor of 100 is applied (10 for inter-species conversion and 10 to protect unusually sensitive individuals), and the result, when multiplied by 70 kg, is 4.1 mg/day for a 70 kg human.

The subchronic inhalation studies with 2-ethoxyethanol summarized in Table 3-4 define NOELS which are higher than the LOAEL for fetotoxicity in rats determined by Doe (1984a). Therefore, the NOEL of 6.8 mg/kg from the Doe (1984a) study may be used to estimate an AIS with assurance that this dose is below effect levels for other subchronic effects. Multiplying by 70 kg and applying an uncertainty factor of 100 results in an AIS of 4.8 mg/day.

The next highest exposure level (50 ppm) which resulted in fetotoxicity may be used to calculate a CS. The animal dose is estimated as 23 mg/kg/day. Application of the cube root of the ratio of the body weight of rats: body weight of humans results in a human MED of 409 mg/day and an RV_d of 1.6. Multiplying by an RV_e of 8 yields a CS of 12.7.

6.1.2.2. OTHER ETHYLENE GLYCOL ETHERS -- Of this subclass of compounds, subchronic inhalation studies have been performed only with ethylene glycol monobutyl ether (see Table 3-5). In humans, 100 ppm (69 mg/kg bw/day) resulted in ocular and respiratory irritation, altered taste and nausea (Carpenter et al., 1956). Ethylene glycol monobutyl ether has also been tested for teratogenicity and fetotoxicity (see Table 3-14). Retarded skeletal ossification was reported in rats at 100 ppm during gestation (Tyl et al., 1984). No effects occurred at 50 ppm corresponding to 44.9 mg/kg bw/day (see Table 3-14 for dose conversions).

A NOEL for guinea pigs of 67.3 mg/kg was defined by Union Carbide (1952), however, the study was of only 6 weeks duration. Dodd et al. (1983) defined a NOEL of 16 mg/kg for rats following 13 weeks of exposure. The

next highest exposure corresponding to either a LOAEL or NOAEL was 49.4 mg/kg. The effects, transient weight depression and depressed red blood cell counts, are difficult to judge because of lack of detail in the reporting. In addition, Werner et al. (1943a) reported a LOAEL of 35.3 mg/kg for the dog following 12 weeks of exposure. In this study only one dose was tested. The NOEL of 16 mg/kg in the rat may be used to estimate an AIS. This dose is below the threshold defined for fetotoxicity. Multiplying by 70 kg and dividing by an uncertainty factor of 100 results in an AIS of 11.2 mg/day.

The inhalation toxicity of ethylene glycol monobutyl ether appeared to be more sensitive in guinea pigs than other laboratory species. A CS was calculated for increased mortality in guinea pigs exposed to 375 ppm (1812.4 mg/m^3), 7 hours/day, 5 days/week for 6 weeks. The intake, assuming guinea pigs inhale 0.23 m^3/day and weigh 0.43 kg, was 202 mg/kg bw/day. Applying the cube root of the ratio of the body weight of guinea pigs to man and applying an uncertainty factor of 10 to convert from subchronic exposure to chronic data results in a human MED of 259 mg/day and an RV_d of 1.9. Increased mortality was assigned an RV_e of 10, and a CS of 19 was calculated as the product of RV_d and RV_e.

6.1.2.3. PROPYLENE GLYCOL ETHERS -- Subchronic inhalation studies suitable for risk assessment were performed with propylene glycol monomethyl ether in rats, monkeys, guinea pigs and rabbits (see Table 3-6). The highest NOAEL below which adverse effects were not reported was 10,000 ppm in rats for 0.5 hours/day over a 79-day period. The corresponding dose was 570 mg/kg bw/day (Rowe et al., 1954) (see Table 3-6 for dose conversion). However, the daily exposure duration in the study is considered inadequate for continuous-exposure risk estimates. Of studies with adequate exposure

duration, Miller et al. (1984) defined the highest NOEL which is below other LOAELS (1000 ppm, 6 hours/day in the rat). In fetotoxicity testing, no effects were produced in rats exposed during gestation at 1500 ppm (1027 mg/kg bw/day Table 3-15). The NOEL of 489 mg/kg bw/day (estimated from 1000 ppm exposure concentration) (Miller et al., 1984) is chosen for derivation of an AIS for propylene glycol monomethyl ether with confidence that protection will also be provided against fetotoxic effects. An uncertainty factor of 100 is applied as discussed previously. The resultant AIS, 4.9 mg/kg/day, corresponds to 342 mg/day for a 70 kg human.

Dipropylene glycol monomethyl ether appears to be more toxic than propylene glycol monomethyl ether when given by inhalation because effects on the liver were observed at doses lower than the NOAEL for propylene glycol monomethyl ether (see Table 3-6) (Rowe et al., 1954). Since effects were seen in rats, guinea pigs, rabbits and monkeys at all levels tested, an AIS for dipropylene glycol monomethyl ether cannot be derived. Therefore, the AIS for propylene glycol monomethyl ether is expected to be protective for that compound, but not for other members of the class propylene glycol ethers or for the class as a whole.

Rowe et al. (1954) observed increased mortality in rats in atmospheres of 6000 ppm propylene glycol monomethyl ether (22,115 mg/m^3), 7 hours/day for 81 days. The intake associated with this exposure is 4791 mg/kg bw/day, obtained by expanding to continuous exposure and assuming that rats inhale 0.26 m^3/day and weigh 0.35 kg. In calculating a CS, a human MED was calculated from the animal intake by multiplying the dose in rats by the cube root of the ratio of the body weight of rats (assumed: 0.35 kg) to humans (assumed: 70 kg) and applying an uncertainty factor of 10 to convert from subchronic to chronic data. A human MED of 5735 mg/day, corresponding to an

RV_d of 1, was calculated. Increased mortality was assigned an RV_e of 10; a CS of 10, the product of RV_d and RV_e, was obtained.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

6.2.1. Oral.

6.2.1.1. 2-METHOXYETHANOL AND 2-ETHOXYETHANOL -- Chronic oral toxicity studies, performed only with 2-ethoxyethanol, include a 2-year dietary study in rats (Morris et al., 1942) and a 103-week gavage study in rats and mice (see Table 3-7). In the gavage study (Melnick, 1984), rats had reduced body weights (both sexes) and apparent adrenal enlargement (males) at 357 mg/kg bw/day, the lowest dose tested. In the feeding study, estimated doses of 725 mg/kg bw/day resulted in testicular damage. Using the lowest LOAEL of 357 mg/kg/day and applying an uncertainty factor of 10 to estimate a NOAEL results in a dose of 35.7 mg/kg/day. This dose level is lower than estimates based on fetotoxicity and hence appropriate for AIC estimation. Applying an additional uncertainty factor of 100 results in an AIC of 25 mg/day.

6.2.1.2. OTHER ETHYLENE GLYCOL ETHERS -- In members of this subclass of compounds, chronic toxicity testing was conducted only with diethylene glycol monoethyl ether in rats and mice (see Table 3-8). Smyth et al., (1964) determined a NOEL of 200 mg/kg/day in a chronic, 3-generation drinking water study. In rats, 1080 mg/kg/day was a LOAEL associated with mild lesions in the liver, kidney and testes of rats, the more sensitive species (Morris et al., 1942). Applying an uncertainty factor of 100 (10 for interspecies extrapolation and 10 for interindividual variability) results in an AIC of 140 mg/day for a 70 kg man.

6.2.1.3. PROPYLENE GLYCOL ETHERS -- Pertinent data regarding the chronic oral toxicity of the propylene glycol ethers could not be located in the available literature. An oral AIC can be calculated for propylene

glycol monoethyl ether, however, by applying an uncertainty factor of 10 to the AIS of 476 mg/day. The resulting AIC for propylene glycol monoethyl ether is 47.6 mg/day. Applying an additional uncertainty factor of 10 to the AIS for propylene glycol monomethyl ether results in an AIC of 47 mg/day.

6.2.2. Inhalation.

6.2.2.1. 2-METHOXYETHANOL AND 2-ETHOXYETHANOL -- The human case studies of exposure to 2-methoxyethanol and 2-ethoxyethanol summarized in Table 3-9 do not quantitate exposure and effect sufficiently to allow the use of these studies in risk assessment. An inhalation AIC for 2-methoxyethanol can be calculated from the TLV of 5 ppm (~16 mg/m^3). Assuming a human inhales 10 m^3/day on the job, works 5 days/week and absorbs 100% of the inhaled dose, an exposure of 114 mg/day is obtained. An AIC of 11.4 mg/day is calculated by applying an uncertainty factor of 10 to protect unusually sensitive individuals. Because this value is larger than the AIS for 2-methoxyethanol, it is not recommended as the AIC. Instead, the AIS for 2-methoxyethanol can be based on the subchronic NOEL of 23.6 mg/kg/day (Miller et al., 1984). Multiplying by 70 and dividing by an uncertainty factor of 1000 results in an AIS of 1.65 mg/day.

Chronic inhalation data for 2-ethoxyethanol are also lacking. The inhalation AIS for 2-ethoxyethanol (4.8 mg/day) was based on concern for fetotocicity which appeared to be a more sensitive endpoint than other subchronic effects. However, fetotoxicity endpoints are not relevant to chronic effects extrapolation unless they occur at doses which appear to be protective for other chronic endpoints. Subchronic inhalation data define a LOAEL of 76 mg/kg/day for the dog (other exposures not tested) (Werner et al., 1943a); a NOAEL of 196 mg/kg/day and a NOEL of 49.9 mg/kg/day for the rat (Barbee et al., 1984); and a LOAEL of 373 mg/kg/day and NOEL of 93.2 mg/kg/day for the rabbit (Barbee et al., 1984). Of these values the highest

NOEL which is below the dog LOAEL is 49.9 mg/kg/day for the rat. Applying an uncertainty factor of 1000 (10 for subchronic duration, 10 for interspecies extrapolation and 10 for interindividual variability) results in 0.0499 mg/kg/day or an AIC inhalation estimate of 3.5 mg.day. Additional toxicological data for non-rodent species would be useful.

6.2.2.2. OTHER ETHYLENE GLYCOL ETHERS -- Studies of the chronic inhalation toxicity of other propylene glycol ethers could not be located in the available literature. For ethylene glycol monobutyl ether, an inhalation AIS of 23.4 mg/day was calculated (see Section 6.1.2.2.). An AIC of 2.3 mg/day can be calculated by applying an additional uncertainty factor of 10. This estimate is lower than that which could be estimated based on the TLV (25 ppm) (ACGIH, 1980).

6.2.2.3. PROPYLENE GLYCOL ETHERS -- Chronic inhalation data regarding the propylene glycol ethers are lacking; subchronic inhalation data sufficient for use in risk assessment are available only for propylene glycol monomethyl ether. An AIS of 399 mg/day was estimated. Applying an additional uncertainty factor of 10 results in an estimated AIC of 40 mg/day. This value is lower than that which could be estimated from the TLV of 360 mg/m^3.

Subchronic inhalation studies indicate that dipropylene glycol monomethyl ether may be somewhat more toxic than propylene glycol monomethyl ether although they were inadequate for AIS estimation (see Section 6.1.2.3.). The ACGIH (1980) has recommended a TLV for dipropylene glycol monomethyl ether of 100 ppm, ~360 mg/m^3. Using the methodology described above, an AIC of 429 mg/day may be calculated from the TLV. Because this value is greater than the AIC for the less toxic propylene glycol monomethyl ether, no AIC for dipropylene glycol monomethyl ether is recommended.

6.3. CARCINOGENIC POTENCY (q_1*)

6.3.1. Oral. No reports of cancer in humans or laboratory animals regarding oral exposure to glycol ethers have been located in the available literature; hence, no q_1* or unit risks for oral exposure can be calculated.

6.3.2. Inhalation. No reports of cancer related to inhalation exposure of humans or laboratory animals to glycol ethers have been located in the available literature; hence, no q_1* or unit risks for inhalation exposure can be calculated.

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APPENDIX

Summary Table for Glycol Ethers

	Species	Experimental Dose/Exposure	Effect	Acceptable Intake (AIS & AIC)	Reference
2-Methoxyethanol					
Inhalation					
AIS	rats	10 ppm, 6 hours/day on days 6-15 of gestation (5.8 mg/kg bw/day)	fetotoxic; NOEL	4.1 mg/day	Hanley et al., 1984a,b; Miller et al., 1983b
AIC	rats	30 ppm, 6 hours/day, 5 days/ week for 13 weeks (23.6 mg/kg)	NOEL	1.7 mg/day	Miller et al., 1984
Oral					
Maximum composite score	mice	31.25 mg/kg bw/day by gavage on days 7-14 of gestation (RV_d=2.2)	teratogenicity (RV_e=10)	22	Nagano et al., 1984
2-Ethoxyethanol					
Inhalation					
AIS	rats	10 ppm, 6 hours/day, days 6-15	fetotoxic; NOEL	4.8 mg/day	Doe, 1984a
AIC	rats	100 ppm, 6 hours/day, 5 days/ week for 13 weeks (49.9 mg/kg)	NOEL	3.5 mg/day	Barbee et al., 1984
Maximum composite score	rats	50 ppm (184.2 mg/m³), 6 hours/ day, days 6-15 (RV_d = 1.6)	fetotoxicity (RV_e = 8)	12.7	Doe, 1984a
Oral					
AIS	rats	46.6 mg/kg bw/day by gavage on days 1-21 of gestation	teratogenic; NOEL	32.6 mg/day	Stenger et al., 1971
AIC	rats	500 mg/kg/day by gavage 5 days/week for 103 weeks	reduced body weight; LOAEL	25 mg/day	Melnick, 1984
Diethylene Glycol Monoethyl Ether					
Oral					
AIS	rats	500 mg/kg bw/day for 90 days in diet	NOEL	350 mg/day	Hall et al., 1966
AIC	rats	200 mg/kg bw/day by the drinking water; chronic; 3 generations	NOEL	140 mg/day	Smyth et al., 1964

APPENDIX (cont.)

	Species	Experimental Dose/Exposure	Effect	Acceptable Intake (AIS & AIC)	Reference
Ethylene Glycol Monobutyl Ether					
Inhalation AIS	rats	25 ppm, 6 hours/day, 5 days/week for 13 weeks	NOEL	11.2 mg/day	Dodd et al., 1983
AIC	rats	25 ppm, 6 hours/day, 5 days/week for 13 weeks	NOEL	1.1 mg/day	Dodd et al., 1983
Maximum composite score	guinea pigs	375 ppm (1812.4 mg/m³), 7 hours/day, 5 days/week for 6 weeks (202 mg/kg bw/day) (RV_d=1.9)	Increased mortality	19	Carpenter et al., 1956
Propylene Glycol Monomethyl Ether					
Inhalation AIS	rats	1,000 ppm for 6 hours/day 5 days/week for 13 weeks	NOEL	342 mg/day	Miller et al., 1984
AIC	rats	1,000 ppm for 6 hours/day 5 days/week for 13 weeks	NOEL	34.2 mg/day	Miller et al., 1984
Oral AIS	rats	949 mg/kg/administered by gavage 5 days/week over 35 days	NOEL	474.5 mg/day	Rowe et al., 1954
AIC	rats	949 mg/kg/administered by gavage 5 days/week over 35 days	NOEL	47.4 mg/day	Rowe et al., 1954
Maximum composite score	rats	6000 ppm (22,115 mg/m³), 7 hours/day for 81 days (479 mg/kg bw/day) (RV_d=1)	Increased mortality (RV_e=10)	10	Rowe et al., 1954
Propylene Glycol Monoethyl Ether					
Oral AIS	rats	680 mg/kg bw/day/administered in the drinking water for 30 days	NOEL	476 mg/day	Smyth and Carpenter, 1948
AIC	rats	680 mg/kg bw/day/administered in the drinking water for 30 days	NOEL	47.6 mg/day	Smyth and Carpenter, 1948

NR = Not reported